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BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

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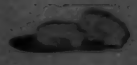

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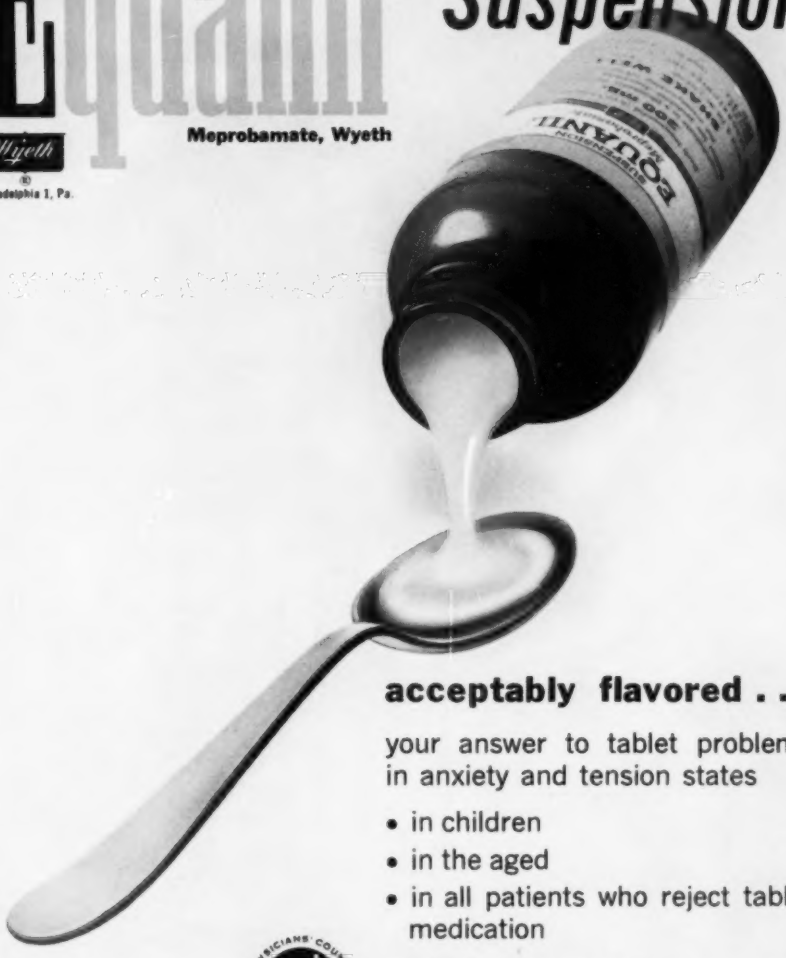

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1. Landes, R. P. and Peters, M. Postgrad. Med. **23**:648, June 1958.

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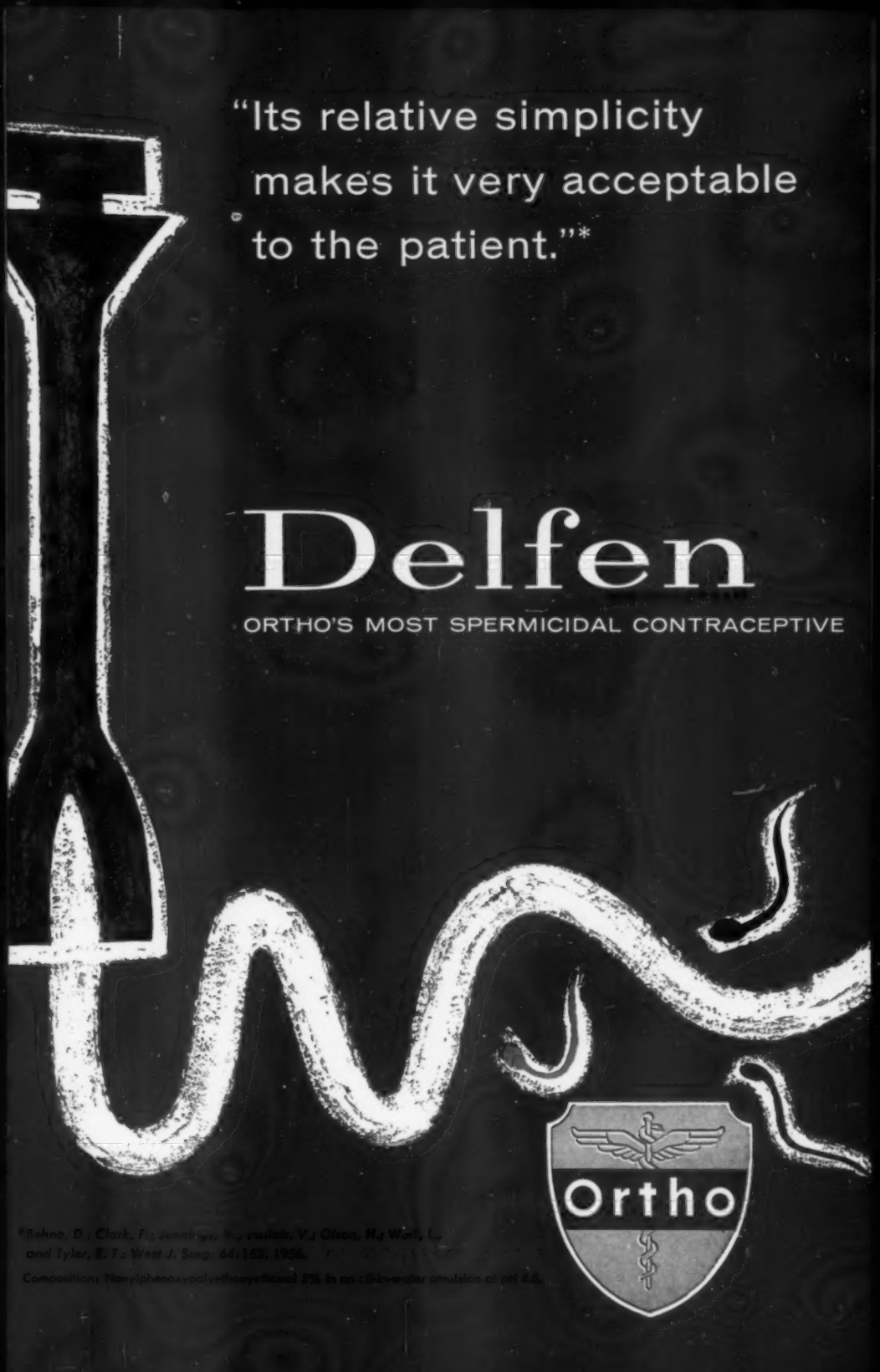
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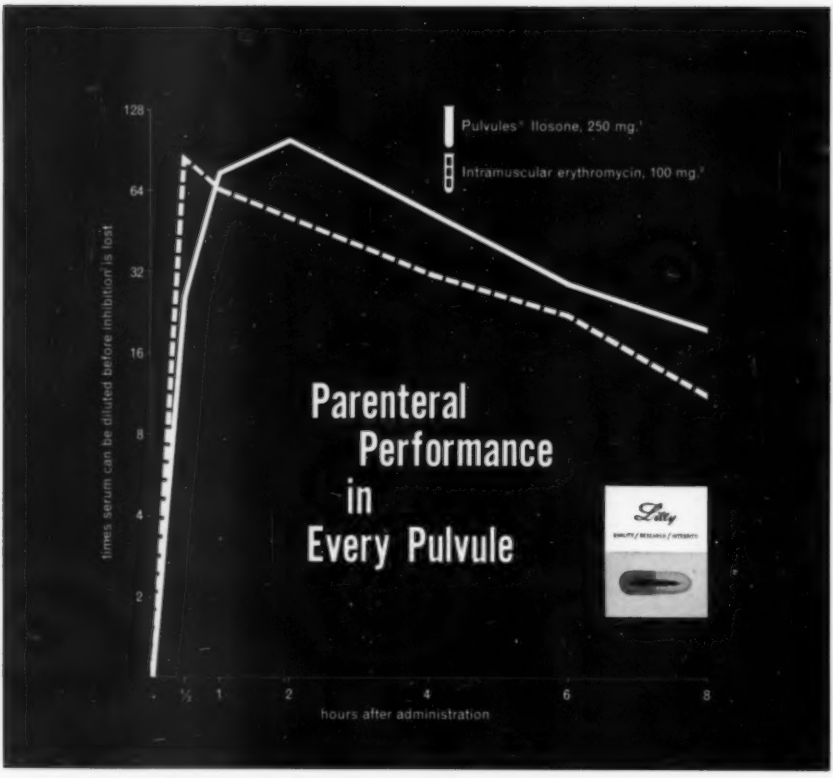

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1. Antibiotic Med. & Clin. Therapy, *5*:609, 1958.

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ROBERT L. CRAIG, *Editor*

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

VOL. 35, NO. 3 MARCH 1959

HEREDITARY DISORDERS OF CONNECTIVE TISSUE*

VICTOR A. MCKUSICK

Associate Professor of Medicine, Johns Hopkins University School of Medicine; Physician, Johns Hopkins Hospital, Baltimore, Maryland

AT LEAST five conditions appear to be hereditary and generalized derangements of one or another element of connective tissue[1]: The Marfan syndrome, the Ehlers-Danlos syndrome, osteogenesis imperfecta, pseudoxanthoma elasticum, and the Hurler syndrome. Each appears to be due to a simple mutant gene, or, possibly better said, a pair of mutant genes at a single locus, since two of these conditions behave as "recessives." I will use the terms "recessive" and "dominant" with the reservations which Dr. Childs** indicates are necessary.

THE MARFAN SYNDROME

You will recall that the victim of the Marfan syndrome is likely to show abnormalities in three areas: in the eye, especially dislocation of the lenses; in the skeletal system, particularly unusual length of the extremities; and finally, in the cardiovascular system, especially a weakness of the media of the aorta, which may lead to diffuse aneurysm of

* Presented at the Second Annual Postgraduate Week, *Research Contributions to Clinical Practice*, of The New York Academy of Medicine, October 14, 1958.

** Presented at the same meeting: Childs, B., Heredity Aspects of Disease, *Bull. N. Y. Acad. Med.* 35:77-86, 1959.

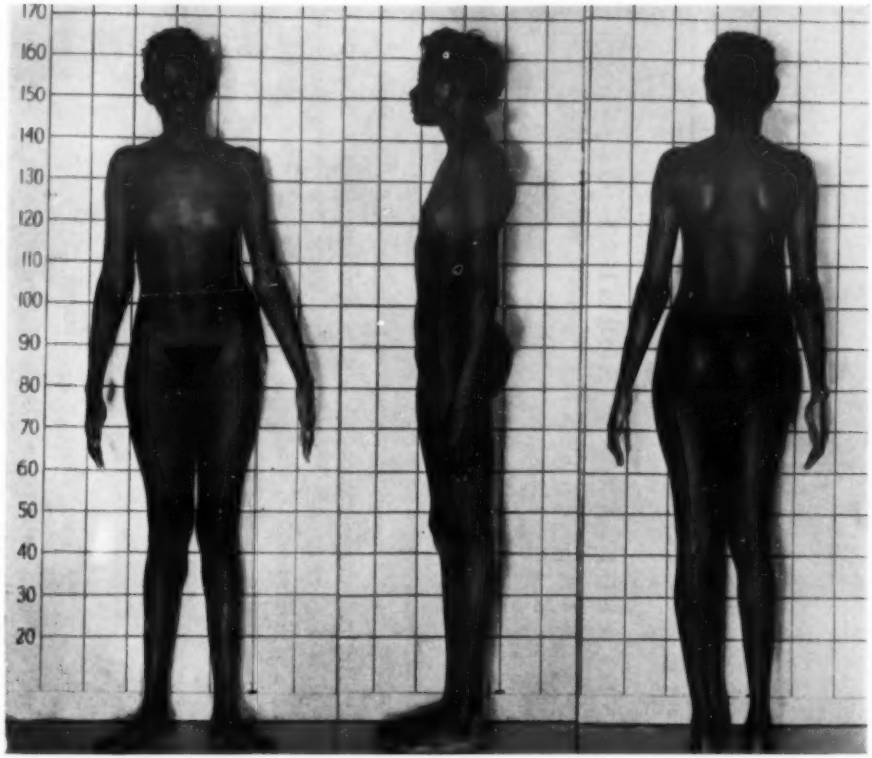

Fig. 1—Habitus typical of the Marfan syndrome. G.H. (815634), age 15 years, has bilateral subluxation of the lenses and spinal curvature. Clinical signs of ventricular septal defect are corroborated by data of cardiac catheterization (courtesy of Dr. Donald Nelson, D. C. General Hospital, Washington). In my personal experience this is the only case of ventricular septal defect in a patient with Marfan syndrome.

the ascending aorta, to dissecting aneurysm, or to a combination of these two.

Figure 1 shows an example of the typical body proportions. Characteristically, the lower segment, measured from the pubic symphysis to the sole, is in excess of the upper segment. In adults this ratio is usually approximately 1. Unfortunately, like all other measurements which may be used as diagnostic criteria in the Marfan syndrome, this is non-specific. There is much overlap with the normal. It is true that if the body proportions in a given individual deviate significantly from those in other members of the family, the impression that the Marfan syndrome is present is strengthened. However, the diagnosis can rarely be made with conviction on skeletal features alone.

In the eye, the lens is most often dislocated upward; its margin may be visible at the lower rim of the pupillary opening. A tip-off to the presence of dislocated lens may be tremor of the iris, so-called iridodonesis. In many cases, full dilatation of the pupil and even examination with the slit lamp are necessary to demonstrate mild dislocation.

In the aorta, a diffuse dilatation of the ascending aorta is a leading feature. In the early stages of life the aorta is normal clinically, and possibly even anatomically it may show no definite abnormality; but there is an innate weakness none the less. With the passage of time and with the particular physiologic stress to which the ascending aorta is exposed, it tends to undergo dramatic changes. Aortic regurgitation develops and the ill effects of that are felt on the heart.

A point of some general clinical importance is the fact that in this condition the part of the aorta first to undergo dilatation is its very base, in the region of the sinuses of Valsalva, down within the radiologic silhouette of the heart, so that a patient may have rather impressive clinical signs of aortic regurgitation, yet show no x-ray evidence of dilatation of the ascending aorta. By following up all the cases of ectopia lentis available to us, we found five cases of patients who have aortic regurgitation without evident cause other than the Marfan syndrome, and who show no x-ray evidence of dilatation of the aorta.

The other type of change that may occur in the aorta is dissecting aneurysm. Often, both diffuse dilatation and later, dissection, are associated in the same aorta.

The ascending aorta seems to be exposed to a particular type of hemodynamic stress that leads to what may be termed "wearing-out".

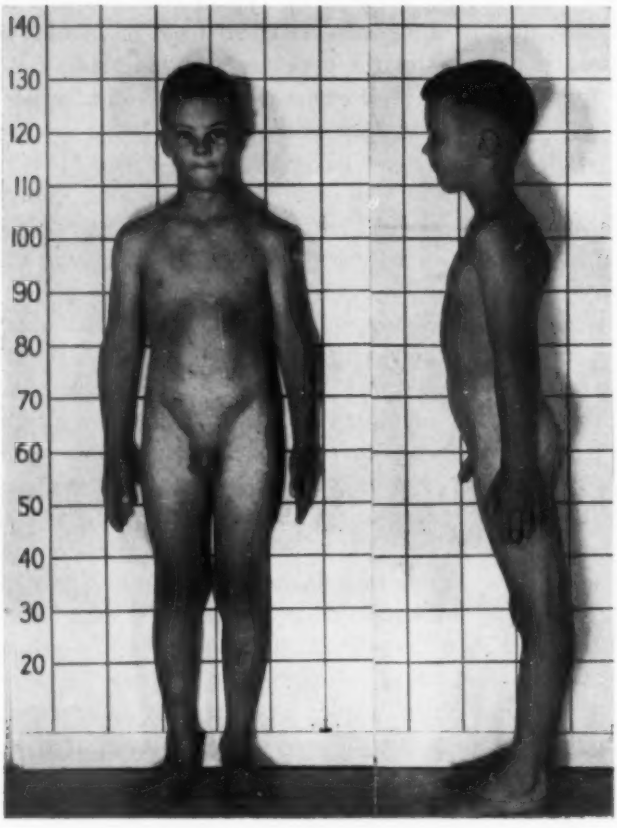

Fig. 2—The Ehlers-Danlos syndrome. R.R. (B53739), age eight years and nine months, shows characteristic pre-tibial scarring, mild genu recurvatum, flat feet, looseness of the soles. The skin generally is abnormally stretchable and the joints hypermobile. Easy bruisability was the presenting complaint. An epicanthal fold (2C), which is not present in unaffected members of his family, is a frequent finding in this syndrome, as is also mild retardation of growth. The characteristic scars are evident also on the forehead and right side of the face. Bilateral inguinal hernias and an umbilical hernia were repaired at the age of two years. No other members of the family are definitely affected. The patient has four brothers and no sisters. One brother had pectus excavatum severe enough to warrant surgical repair, and a second brother has mild pectus excavatum.

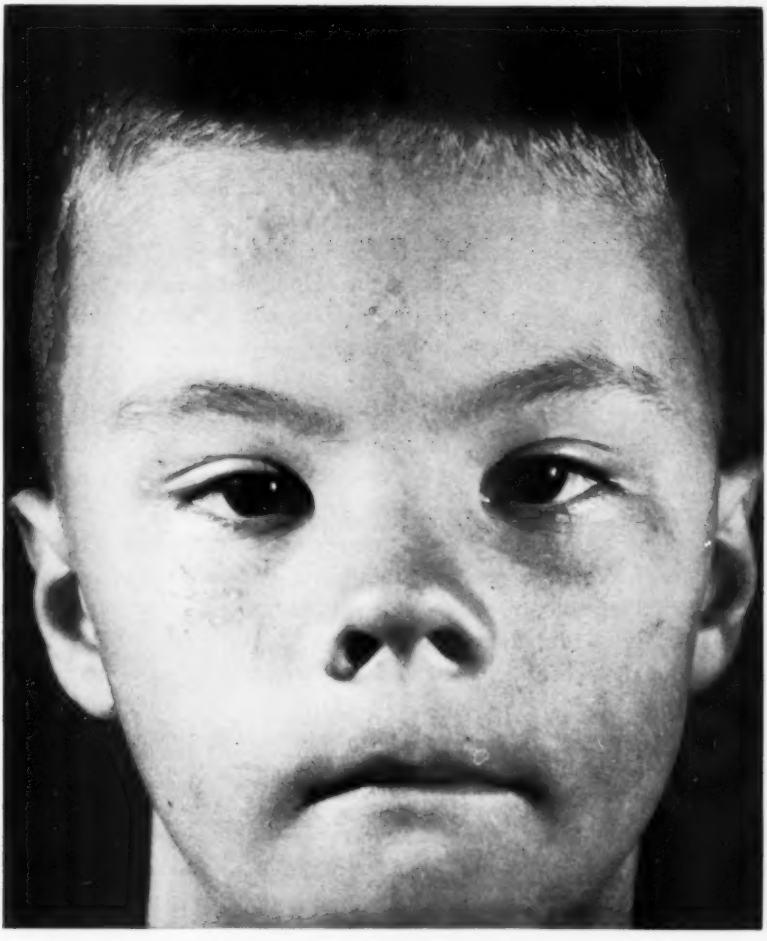

Fig. 2C—(see opposite page)

Expansile pulsation is particularly striking in the aorta proximal to the arch. This expansile pulsation with each heart beat, over a long period of time, seems to be responsible for "structural fatigue" in the aortic wall and the changes that one observes. Thus one can account for the fact that the ascending aorta is predominantly involved in the Marfan syndrome, despite the likelihood that the connective tissue defect, whatever

its exact nature, extends throughout the aorta. We have observed a single instance of involvement of the abdominal aorta without involvement of the thoracic aorta[2].

In the Marfan syndrome, inheritance seems to be that of an autosomal dominant trait. One sees fairly frequently individuals who seem to represent new mutations. One cannot discover evidences of disease in other members of the family. (Some might be phenocopies, facsimiles due to non-genetic cause that we do not yet understand. Possibly, some are due to a different gene inherited as a recessive. Some may, in fact, have affected parents who, by our crude methods, cannot be distinguished from the normal. But the view that most of these are new mutations seems most likely.) Some of such cases are very severely affected. In one, for example, marked aortic regurgitation was already present at two years of age, together with pronounced skeletal and ocular changes[2].

Diagnosis in many cases of suspected Marfan syndrome is difficult. The range of the grade of severity is wide, a general characteristic of "dominant" conditions. Aortic regurgitation in persons of rather gangly habitus may suggest the diagnosis of the Marfan syndrome. In such cases there are perhaps two things one can do to strengthen the diagnosis: one should investigate the family as fully as possible for the presence of more definitely affected members, and should examine the patient's eyes with the slit lamp, with full mydriasis, for evidences of even mild dislocation of the lenses. If both of these investigations are negative one simply cannot say, in the present unsatisfactory state of our knowledge about this disease, "yes" or "no" to the question of the presence of the Marfan syndrome. Obviously, discovery of a chemical abnormality[3, 4] would not only have important implications as to the basic defect but would have diagnostic usefulness as well. It is worth while to point out the lack of specificity of skeletal changes; there are phenocopies, facsimiles of the skeletal proportions which can occur on other bases. First, there are anthropologic bases. There are African tribesmen, for example, who have body proportions rather like those of the Marfan syndrome. Secondly, there are pathologic conditions which can simulate; the eunuch and the patient with sickle cell anemia have body proportions suggestive of the Marfan syndrome. The gracile habitus of many patients with atrial septal defect may lead to a mistaken diagnosis of the Marfan syndrome.

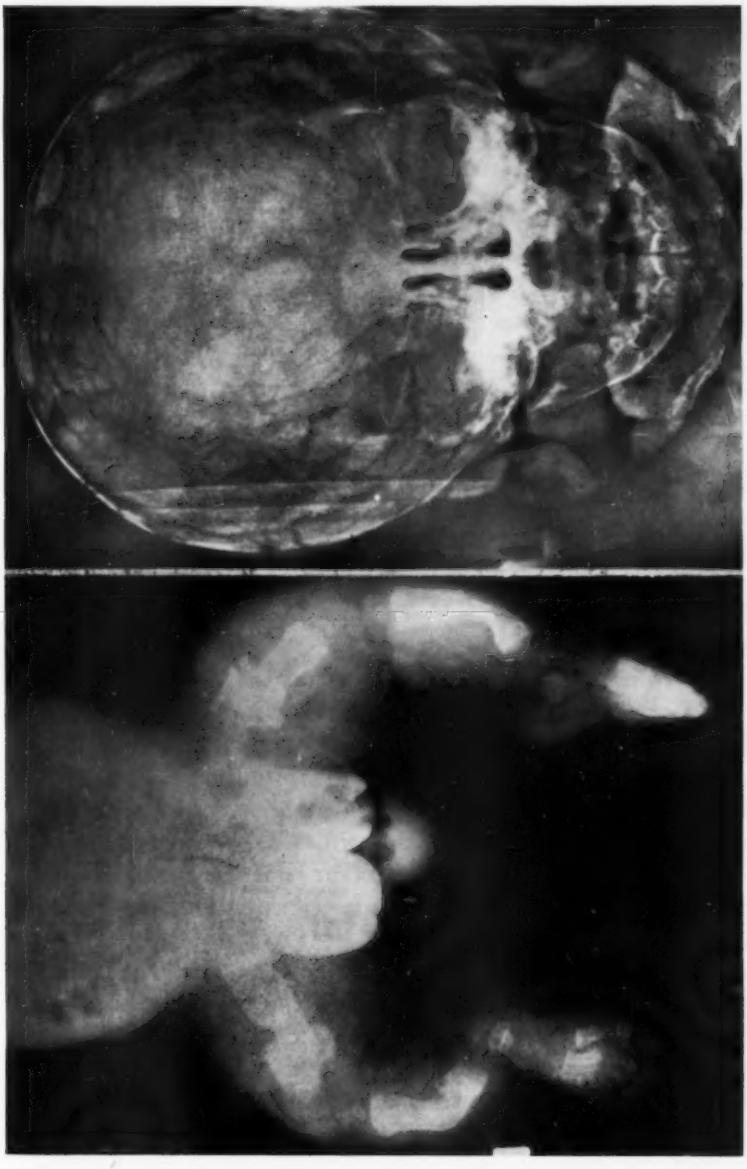

Fig. 3—"Congenital" osteogenesis imperfecta in K.K. (A95443), age two and one-half weeks. A. Multiple fractures, bowing of the extremities, and bilateral inguinal hernias are evident. B. Demonstration of multiple Wormian bones in the *caput membranaceum*.

What is the nature of the basic defect in the Marfan syndrome? One gets the impression from the examination of the aorta that the elastic fibers are basically defective in such a way that they undergo deterioration with the passage of time. What does the suspensory ligament of the lens have in common with the media of the aorta? The suspensory ligament seems to be largely collagenous in nature (although unusual in that chymotrypsin digests it) and the aorta has more collagen than elastic tissue[5]. The defect might be in the collagen, and the elastic tissue changes might be secondary ones. One then has to explain, of course, the excessive longitudinal growth of the long bones of the extremities (and seemingly of the ribs, resulting in chest deformities, sometimes marked pigeon breast, sometimes inward displacement of the sternum, pectus excavatum). Possibly the defect is in the periosteum. One wonders whether there is an unreining of longitudinal growth due to some connective tissue defect of the periosteum. This is clearly all speculation.

The Ehlers-Danlos Syndrome

A Dutchman by the name of Job van Meekeren in the 1600's described an extraordinary Spaniard who could pull the skin of his chest out to a considerable distance; on release, the skin sprung back to its original position. This was probably the earliest description of the Ehlers-Danlos syndrome.

In this condition (Fig. 2) there is hypermobility of the joints and hyperelasticity of the skin. The skin is also excessively fragile, so that with even minor trauma it breaks into widely gaping wounds. Characteristic "cigarette-paper" scars develop at sites of trauma. The internal medical manifestations of this disease are only beginning to be explored, but it does seem to be clear that hiatus hernia is fairly common and that diverticula of the gastrointestinal tract occur rather frequently. Possibly cardiac and aortic abnormalities occur in this condition, but that possibility requires better working out.

Superficially, superabundance of elastic fibers might seem to account for the hyperelasticity of skin and joints. However, there are suggestions that the defect here involves the way that the collagen bundles are put together into a firm wicker-work. It is the collagen wicker-work that determines how extensible the joints are or how stretchable the skin is. It is thought that, whereas in the normal the collagen wicker-work is dense, it is more loosely meshed in the Ehlers-Danlos syndrome.

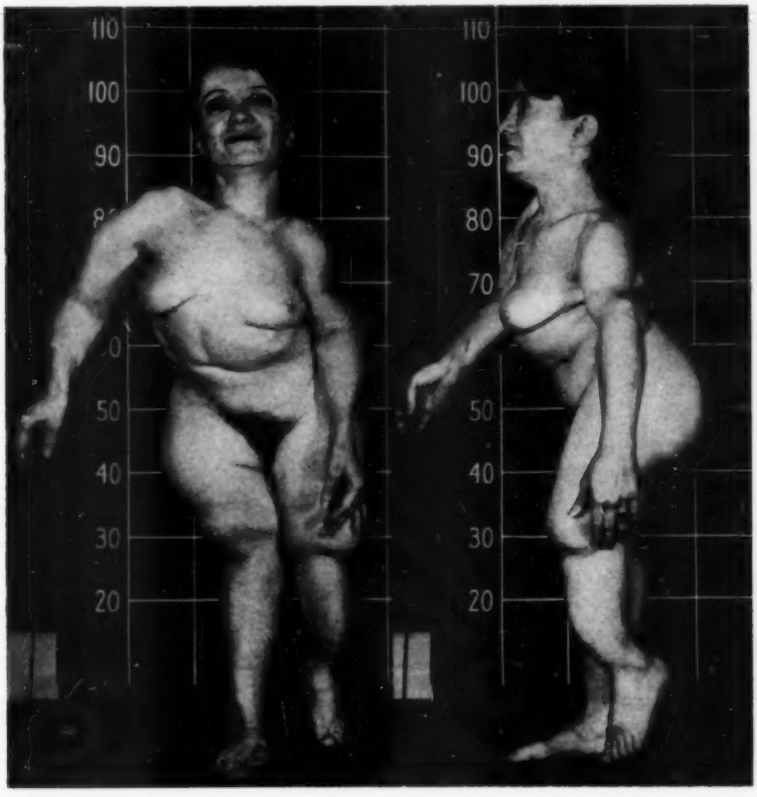

Fig. 4—Osteogenesis imperfecta in K.C. (673043), age 35 years. Innumerable fractures have occurred, the first having been recognized at the age of nine months. The sclerae are blue; hearing is intact. The patient is scarcely taller than a four year old child. She has never walked and is carried about by a husky female friend. Of two pregnancies, one was terminated for therapeutic reasons and the other ended in spontaneous abortion.

The evidence for this is based on fresh wet preparations of subcutaneous tissue. In biopsies prepared by the usual histologic technique, one gets an impression of a looseness of the collagen bundles. In some cases there is indeed some excess of elastic fibers. This may, however, be a secondary phenomenon. It is possible that hyperplasia of the elastic fibers is stimulated by the excessive stretching to which the tissues are exposed.

The Ehlers-Danlos syndrome is probably inherited as a "dominant".

Fig. 5—Skin changes of pseudoxanthoma elasticum in C.T. (582989), 32 year old man. The skin is lax, ridged and grooved with a yellowish tint (hence "pseudoxanthoma"). The patient has had a total of about 15 massive gastrointestinal bleeds necessitating hospitalization and transfusion. No specific bleeding site has ever been identified.

Since diagnosis of the skin and joint changes when mild is rather subjective, the genetics is not completely certain.

Osteogenesis Imperfecta

This is one of the more familiar of these syndromes. It is clearly a generalized condition, not limited to bone. It is a disorder, first, of the organic matrix of bone, leading to the classical liability to fractures; secondly, of the sclera, producing blue scleras; and thirdly, of other soft tissues, resulting in loose-jointedness, hernia, "thin skin" and other manifestations. The dentine of the teeth is likely to be affected. For some unknown reason, the lower incisors show greatest stunting and discoloration. Progressive deafness is also a frequent feature.

Figure 3 shows an x-ray of a severely affected infant. Here one sees evidence of hernia, which rather frequently accompanies this condition. Caput membranaceum with multiple Wormian bones is also demonstrated. Dwarfism is the rule in more severely affected cases (Fig. 4).

Osteogenesis imperfecta may not be a homogeneous entity; and until we have knowledge of the basic defect and the ability to test for that defect, we cannot be certain that we are dealing with one entity. Many of the pedigrees seem to fall into a dominant pattern of inheritance. Some severely affected infants are born into families in which other cases have not occurred. These are cases of so-called congenital osteogenesis imperfecta (Fig. 3). They may represent new mutations at the same locus as determines the disease in families with multiple affected cases.

Pseudoxanthoma Elasticum

In pseudoxanthoma elasticum, the skin, particularly in the flexural areas of the neck, axilla, and groin, is affected with degenerative changes, coming on in some cases not until the third decade, in others considerably earlier. The situation is probably comparable to that of the aorta in the Marfan syndrome, in that there is an inborn weakness of some connective tissue element and that with wear and tear in the flexural areas, deterioration of a specific type sets in. Bruch's membrane of the fundus of the eye undergoes cracking, so that one sees angioid streaks, vessel-like streaks, coursing across the fundus. Scar tissue grows into the fundus, leading, together with the bleeding which may occur in the eye, to severe impairment of vision. This is a condition of considerable importance to the internist because massive gastrointestinal bleeding occurs as a consequence of the same type of connective tissue change in the intermediate-sized and smaller blood vessels of the gastrointestinal tract. Furthermore, the peripheral arteries undergo medial degeneration and calcification. Arterial insufficiency, both peripheral and coronary, is sometimes a significant clinical feature.

Skin biopsy reveals in the deeper parts of the corium large amounts of material which stains like elastic tissue. However, there is a school that thinks this is degenerated collagen which assumes the tinctorial characteristics of elastic tissue. By this view, pseudoxanthoma elasticum is a hereditary variety of "elastotic degeneration" of collagen. This matter has not yet been fully settled[6]. The disease behaves as an autosomal recessive.

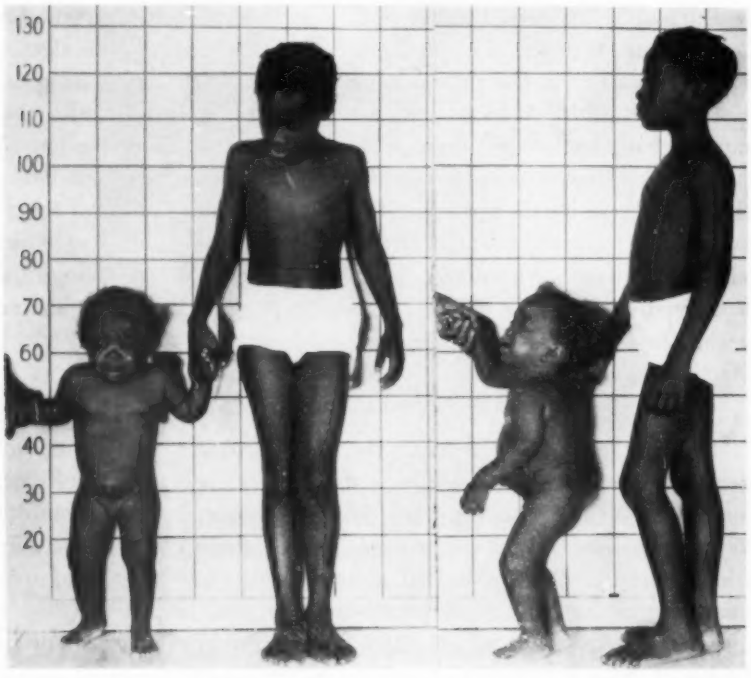

Fig. 6—The Hurler syndrome. On the left of each view: C.D. (B41371), age two and one-half years, is a member of the only Negro family with the Hurler syndrome I have seen. The head is large and the facies characteristic of the Hurler syndrome. The elbows, shoulders, knees and other joints show reduced mobility, preventing full extension. The hands are short and the terminal phalanges cannot be fully extended. Both the liver and the spleen are enlarged. Nasal breathing is obstructed by a continuous mucopurulent discharge. Both corneas are clouded. Of six children, three—two boys and this girl—have been affected with the autosomal recessive form of the Hurler syndrome. A normal eight year old sister is also shown here. The two other affected children died at the ages of three and four years.

The Hurler Syndrome

I shall close this survey with a consideration of the Hurler syndrome (gargoylism), which in recent years has come to be viewed as an abnormality of mucopolysaccharide. The non-cerebral manifestations include a characteristic dysostosis, dwarfism, stiff joints (claw hands, reduced mobility of large joints), and hernia (Figs. 6 and 7). Furthermore, the liver and spleen become enlarged due to deposit of mucopolysaccharide. Similar deposits occur in the intima of the cardiovascular

Fig. 7—Previously unpublished photograph of the cases Hunter described in 1917 (5). The younger brother (G.B.C., born 1907) died in 1918 of pneumonia, and the elder one (R.W.C., born in 1904) died in 1920 of "dropsy." The youngest sibling was apparently unaffected. The characteristic facies and "claw hands" are evident. These brothers are thought to have had the sex-linked recessive form of the Hurler syndrome. The young sister shown here is unaffected. (Photographs and follow-up information, courtesy of Drs. Nancy Gemmell and L. G. Bell, University of Manitoba, Winnipeg.)

system,—in the coronary arteries, for example. These deposits may lead to angina and to sudden death. Abnormality of the heart valves results in systolic and diastolic murmurs. The cerebral aspect of the disease, manifested mainly as progressive impairment of mental function, has not been correlated, to our complete satisfaction, with the non-nervous-system aspects. It is possible that an enzymatic mechanism, common to brain and connective tissue, is faulty. Or one of the mucopolysaccharides produced in excess may be toxic to the brain. Hydrocephalus (from involvement of the meninges) often contributes to the cerebral damage but is clearly not the "whole story".

Large amounts of chondroitin sulfate B and heparitin sulfate are excreted in the urine[7]. Normally these are excreted in insignificant amounts. This discovery not only has important implications for the basic defect but also is already proving a useful diagnostic test in borderline cases.

There are two genotypes of the Hurler syndrome, and the corresponding phenotypes are slightly different. The more frequent form, inherited as an autosomal recessive, is almost always accompanied by clouding of the cornea and tends to be more rapid and severe in its evolution. In the less frequent sex-linked recessive variety (behaving genetically like hemophilia), clouding of the cornea probably never occurs and the patient may live to an older age (the 20's, or even later). The patients described by Hunter[8] in 1917 were probably of the latter genetic type (Fig. 7).

In concluding, one might say that it is possible by means of clinical analysis, supplemented only by conventional pathological methods, to go a considerable distance toward unraveling some of these complex hereditary syndromes. However, it should be pointed out that much remains to be done toward defining the basic defect in each. With none of these disorders are we nearly as far along as we are in the case of some of the beautiful examples about which Dr. Childs* and Dr. Janeway** have told you.

* Presented at the same meeting: Childs, B., Hereditary Aspects of Disease, *Bull. N. Y. Acad. Med. 35*:77-86, 1959.

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AN INTERNIST LOOKS AT GASTRIC ULCER*

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IF ONE ADOPTS the attitude that every gastric ulcer should be treated surgically, a discussion such as the present one is superfluous. With full realization of the risk involved to the patient, I believe that it is the duty of the internist to make every effort to exclude from surgery any gastric ulcer in which the preponderance of evidence favors a benign lesion. There will be mistakes, but we must balance those mistakes against the not unimportant considerations of mortality and morbidity of gastric surgery. In connection with mortality statistics, we must keep in mind not those quoted in the best surgical clinics in the country, but the expected mortality in the average hospital, in which the vast majority of gastric cases are operated in this country. The morbidity of gastric surgery even in the hands of the most experienced surgeons requires some comment. An inevitable group of cases with dumping syndrome, postgastrectomy steatorrhea, iron deficiency anemia, and various other deficiency states, all of which may be condoned in the presence of necessary surgery, imposes an intolerable penalty upon the patient on whom unnecessary surgery is performed.

We realize that, in the final analysis, the differential diagnosis between a benign and malignant gastric ulcer represents an educated guess. The major decision in such a lesion is to exclude early malignancy. The best surgical results with gastric malignancy naturally occur in early cases and we must not be responsible for delay in such instances. If the gastric ulcer is very large, over 4 cm. in diameter, the decision about surgery is not too difficult. A benign lesion of that size usually will not heal satisfactorily, and may require surgery in its own right. In a malignant lesion of that size, there probably will have occurred lymphatic spread of such a degree as to preclude a surgical cure.

* Presented at the Stated Meeting of The New York Academy of Medicine, March 6, 1958. Scientific program on *Gastric Lesions*, arranged by the Sections on Medicine and Surgery.

The problem of ulcer versus carcinoma of the stomach centers about the *small* gastric lesion, in which the ulcer is *under* 4 cm. in diameter. In a somewhat dogmatic way, I shall try to give my own interpretation of the factors which I use to make a decision with reference to surgery. This is an individual matter and will vary from doctor to doctor, depending on his experience with certain techniques, and the availability of others.

1. Does the *history* of the patient in any way help us in making this diagnosis: not entirely, but it is of some value. The patient over age 50 years in whom gastric distress occurs for the first time is more of a prospect for malignancy than one who has had symptoms of peptic ulcer for many years, with previous roentgen demonstrations of ulcer-like lesions of the stomach or duodenum. Rhythmic epigastric distress with food and alkali relief suggests a benign lesion, but does not exclude malignancy. Recent severe gastric hemorrhage is more characteristic of a benign rather than a malignant ulcer.

2. The physical examination rarely aids in the recognition of early gastric malignancy.

3. The *roentgen* examination is the most important single study in the differential diagnosis of benign and malignant gastric ulcers.

Benign gastric ulcers as a *group* possess certain roentgen characteristics which help us to differentiate them from early cancerous ulcers. These characteristics, variously stressed by different observers, concern the location and appearance of the ulcer and the nature of the adjacent stomach.

A benign ulcer most commonly is located in the vertical portion of the lesser curvature. A greater curvature gastric ulcer statistically is more likely to be malignant, but this is not so invariably true as to make the diagnosis mandatory by position alone. Greater curvature ulcers must be evaluated on the basis of their appearance, apart from location. Prepyloric and antral ulcers usually are not so clearly defined on roentgen films as those in the saddle area. The smaller diameter of the prepyloric area often adds to the difficulty of clearly outlining the ulcer and obtaining a clear idea of the character of the adjacent gastric wall.

A benign ulcer usually presents as a *projecting niche* beyond the stomach proper. Hampton's sign, a thin lucent line with parallel straight margins, across the neck of an ulcer crater, is caused by the overhanging edge of mucosa. The Hampton sign almost never occurs in malignant

ulcers. The collar of the benign ulcer is smooth and even. The ulcer base should be smooth. There should be no masses in the adjacent area. While the *size of the ulcer* is not so important from the point of view of differentiation of malignancy, we generally urge surgery with the larger ulcers for reasons other than the possibility of malignancy.

Radiating folds of gastric mucosa converging on the ulcer are fairly characteristic of a benign lesion. One must watch out for *nodularity* and *stiffening of the gastric wall in the immediate vicinity of an ulcer.* Such a finding suggests malignancy, and the absence of such findings points toward a benign lesion.

A malignant ulcer may be present anywhere in the stomach. The ulcer itself generally is *flatter* in the malignant type. There may be some rigidity around the crater in the adjacent gastric wall. The meniscus sign is not too commonly seen in its typical form, but an ulcer located on a mound is quite characteristic of malignancy. One rarely sees radiating folds converging toward a malignant ulcer. The irregularity of the adjacent gastric wall will more likely indicate malignancy. The remaining portion of the stomach in malignant ulceration may show no alteration.

Apart from those lesions which roentgenographically show fairly definite evidence suggesting their benign or malignant character, there is a group of lesions in which roentgenologists refer to "*indeterminate*" findings, in which it is impossible to rule out malignancy definitely. Such lesions may be *better regarded as malignant* from the point of view of management.

The presence of a *duodenal ulcer* in a patient *with a gastric ulcer* favors the probability of a benign gastric lesion, but this generalization is not absolute in every instance, and the diagnosis finally must rest on the characteristics of the gastric lesion itself.

Multiple ulcers in the stomach statistically are more likely to be benign. I reported two such cases, in each of which there were three separate gastric ulcers, all benign, and all, incidentally, on the greater curvature of the stomach.

4. A gastric analysis is an important adjunct in the decision with reference to malignancy. I subscribe to the idea that in the presence of achlorhydria, any gastric lesion, especially an ulcer, is to be regarded as malignant until proven otherwise. For this purpose, we utilize the conventional bread and water meal. If achlorhydria is present, histamine

stimulation is used. The problem arises not in patients with achlorhydria, but in those with free hydrochloric acid in the stomach. If any free hydrochloric acid is present, the degree of acidity bears no relation to the probability of the lesion being either benign or malignant.

5. Gastroscopy often furnishes a clue to the diagnosis but the results vary with the experience of the observer. In the Borrmann classification of gastric carcinoma, there are four groups: I. polypoid (2.9 per cent); II. round ulcer (17.6 per cent); III. ulcer with localized infiltration into the surrounding area (16.3 per cent); IV. diffuse infiltration (63 per cent).

Our concern with reference to gastric ulcer has to do with groups II and III of the Borrmann classification and gastroscopy may well be of help in this respect. A typical benign gastric ulcer in appearance suggests an aphthous ulcer of the mouth. The size may vary. The ulcer has regular edges. The base is clean and covered with a whitish exudate. Any deviation from the typical ulcer pattern is to be regarded with suspicion, especially any suggestion of infiltration of the tissues near the ulcer. One may regard with suspicion any irregular ulcer margins, or a piling up of growth in the crater. The radiating folds, also seen roentgenographically, are quite characteristic of benignancy. The carcinomatous ulcer generally has a necrotic base, a bleeding surface, overhanging margins which are nodular, irregular and rigid. The adjacent gastric wall seems somewhat rigid. Unfortunately, there are some areas in the stomach where an ulcer may not be visualized with the gastroscope, especially in the fundus. Gastroscopy is not infallible and mistakes may be made in borderline cases. However, in typical cases, gastroscopists should have little trouble in detecting the true nature of the lesion.

6. Theoretically, an expert cytological study of the removed gastric contents should be productive of a high degree of accuracy in the diagnosis of gastric carcinoma. The results in large polypoid gastric malignancies are good, but not so good in those cases in which we try to differentiate malignant lesions resembling gastric ulcer. The brush techniques represent an advance but so far the results are disappointing. Moreover, the training and experience of the pathologist is an important factor in the accuracy of the test. The report of a grade 4 malignancy in gastric contents is the equivalent of a biopsy and cannot be ignored.

In a patient in whom the preponderance of evidence favors a benign

lesion a medical program will be tried for two weeks. All other cases go to surgery. I believe that the rate of healing generally may be regarded as an index of benignancy. However, I have known proven benign gastric ulcers which failed to heal over a period of five years. These may occur in elderly people, but usually, in those cases, the size of the crater will not vary on repeated roentgen examinations. In general, a benign gastric ulcer in a younger person will heal completely or reduce to a half or a third of its original size, following two weeks of a strict hospital program of bed rest, hourly milk feedings, hourly amphoteric antacid, and the judicious use of anticholinergic drugs and sedation. A rare malignant ulcer may seem to heal partially but this is uncommon in my experience. If a satisfactory state of healing has not occurred after the two-week period in the hospital, operation is recommended. In instances in which the ulcer apparently heals and shortly thereafter recurs, I believe that surgery should be recommended. Early recurrence of the ulcer need not indicate malignancy, but the probability of the benign nature of the lesion begins to decline.

Hospitalization of gastric ulcer patients is a very important part of the program. If one is going to use a strict program over a two weeks' period as a therapeutic index on which to base the decision for operation, the patient should have the advantage of the maximum that we may offer in the way of a medical program.

In my experience, using the plan of attack outlined, the number of instances of malignant ulcer overlooked should be extremely small, and the end results should compare favorably with a program in which indiscriminate surgery is used on all gastric lesions.

In summary, then, on basis of *history*, *roentgen study*, *gastric analysis*, *gastroscopy* and *gastric cytologic study*, if the findings are consistent with a benign ulcer, a strict medical program is adopted. If any of the above studies suggest malignancy, surgery is advised at once without a preliminary medical program. If at the end of two weeks of medical program, the ulcer heals partially or completely, we are encouraged to continue a medical program with frequently repeated x-rays. If the ulcer fails to heal completely within a month, or recurs at any time in the same spot, surgery is urged.

On this plan, I do not think we are exposing the patient to unnecessary surgery and we have been largely successful in eradicating our early cancerous ulcers.

EARLY RECOGNITION OF NEUROLOGICAL CONDITIONS IN A PSYCHIATRIC HOSPITAL*

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There are various neurological or organic conditions which may initially appear in the guise of psychiatric syndromes of the functional type. The psychiatric symptoms thus presented are often explained by the fact that some agent or process has impaired the normal function of the brain tissue with the result that there is a deficit largely in the intellectual capacity. Equally important is the fact that the personality functioning may be sufficiently disturbed or distorted so that the presenting symptomatology may initially be characteristic of a non-organic or functional illness. The appearance of such symptoms may cause a patient to be referred to a psychiatrist or for hospitalization in a psychiatric hospital; and unless the neurological or organic basis for the condition is recognized, it is quite conceivable that a medically or surgically correctible condition may be overlooked until it is too late. On the other hand, an equally significant point is the fact that even if an individual has an unalterable neurological or organic etiology for his condition, the psychiatrist may still play a most important role in helping the patient psychologically with his emotional adjustment to the disease. Furthermore, the psychiatrist may be able to assist the patient's family, friends or employer with their own emotional response to the illness. Certain neurological conditions may also be discovered which have developed as a consequence of, or in association with, a primary psychiatric disorder.

A review of 3,500 cases admitted to the New York Hospital–Westchester Division in the period between January 1, 1945 and January 1, 1955 revealed that about 5 per cent had presented some existing basic or associated neurological condition. The ages of these patients ranged from 15 years to 81 years, with an average age of 48 years. The neurolog-

* Presented at a combined meeting of the Section on Neurology and Psychiatry with the New York Neurological Society at The New York Academy of Medicine, November 11, 1958.

ical conditions appeared with equally relative frequency in men and women. When compared and correlated with the psychiatric diagnoses, there appeared to be no consistent relationship. Among the 5 per cent with positive neurological findings, there was a wide diversification in neurological entities. Lesions of inflammatory and vascular nature predominated, as would be expected; with Bell's palsies, encephalitis, residuals of poliomyelitis, post-encephalitic Parkinsonism, peripheral neuritis and herpes zoster appearing among the inflammatory lesions; with hemiplegias, subarachnoid hemorrhage, and arteriosclerotic Parkinson's syndrome predominating among the vascular lesions. There were still a few luetic conditions, although these are appearing with less frequency. Convulsive disorders, post-traumatic lesions, congenital and degenerative cerebral and spinal lesions, migraines, hypocalcemic tetany and post-hypoglycemic encephalopathy were observed. New growths and space-occupying lesions were, of course, among the more dramatic findings. In the latter conditions the need for early recognition is obvious, and yet these are often well disguised by the psychiatric phenomena initially presented. Following suicidal attempt, lesions of the peripheral nervous system, such as injury to the ulnar nerve, may often be disguised and determined only on careful examination.

The presenting psychiatric symptoms were carefully reviewed, particularly in those cases in which a diagnosis of brain tumor was made, to determine whether there were any features which might be characteristic or indicative of the underlying neurological condition. As has been reported earlier by Jameison and Henry[1], such could not be found. We would agree with these authors, however, that "When in distress from physical suffering the psychotic patient is no different than any other. He either prefers to be left alone or he is appealing for help. Whenever he indicates through his complaints or his behavior that the distress is within his head he speaks as loudly as he would if he were normal and he should be heard providing the physician is not distracted by the manifestations of the psychosis". The following case reports may well prove to be of considerable interest:

Among the patients admitted to the New York Hospital-Westchester Division in 1945 was a male civil service employee of 51 years of age. He was married and had been a faithful government employee for 28 years, with a satisfactory health record. Two years prior to his admission to the hospital, his previously active interest in community

affairs gradually began to deteriorate. A year later it was noted that he was losing weight, that his appetite was poor and, with his increasing weakness, he developed a tendency to fall. Eight months prior to admission he sustained a head injury, following which he was dazed but able to continue his work. Four months prior to admission he was referred to a general hospital but was dismissed following a work-up which revealed a low basal metabolic rate and a latent kidney stone. He was, however, unable to return to his work from that point onward. Gradually he became increasingly disoriented and, later, incontinent of urine and feces. He also appeared depressed. Consequently he was referred for electric shock treatments, of which he received seven, resulting only in added confusion. Following that series of treatments he was referred to the New York Hospital-Westchester Division. On admission he was disoriented, emaciated, weak and unsteady. He swallowed with great difficulty and required tube feeding. He appeared dull, mumbled to himself unintelligibly, and was incontinent. Ophthalmoscopic examination revealed no papilladema. X-ray of the skull revealed some flattening of the sella-tursica but was otherwise negative. There was one cell in the cerebral spinal fluid with a total protein of 75 and an elevated first zone colloidal gold curve. The blood and spinal fluid Wassermanns were negative. He gradually became semi-comatose, and neurological consultation was sought. This latter examination revealed no evidence of increased intracranial pressure, but by this time he had bilaterally positive Babinskis. The dysphagia was still present and he had absent abdominal reflexes. It was considered that a differential diagnosis lay between pseudo bulbar palsy and, possibly though doubtfully, multiple sclerosis. At that time it was further observed that the deep reflexes on the right were slightly exaggerated. X-ray of the chest revealed questionable areas of bronchiectasis, but was otherwise negative. The patient grew progressively weaker, the semi-coma lapsed into full coma, and one month after admission he expired. The post-mortem examination revealed the following findings: There was an encapsulated and vascular mass, four centimeters in length, occupying the entire right frontal pole of the brain, which proved upon microscopic examination to be a meningioma. Nephrolithiasis of the left kidney and a broncho-pneumonia of the right lung were also found. With the progressive history definitely pointing to organic brain disease, but accompanied by dysphagia, with an absence of signs of increased intracranial pressure,

in a man of 51 it was easy to be led into an acceptance of a diagnosis of cerebral arteriosclerosis and pseudo bulbar palsy. With more recently developed techniques a more accurate conclusion might have been reached, but the dominance of the psychiatric picture was sufficient at that time to carry the day.

Ten years later a 39 year old married professional man was admitted to the New York Hospital-Westchester Division with a history of excessive indulgence in alcohol for a period of more than five years. It was further learned that about three weeks prior to his admission to this hospital, he had been persuaded to seek help for his alcoholic problem while in a distant city. He had been "partially inebriated" when he had reported for that consultation, and three days later it had become necessary for the physician to see the patient at his hotel following a bout of heavy drinking. At that time he was confused and looking for smoke and glass on the rug. Obviously unable to look after himself, he was placed in a hospital, where an examination revealed a positive Babinski reflex and ataxia to the right. His speech was slurred, and sensorium clouded. He complained of intermittent blurring of vision and diplopia on lateral gaze, mainly to the right. There was evidence of a left ulnar peripheral neuritis. Within a few days he was much improved and was returned to his home with the advice that he seek institutional help for his alcoholism. Ten days before admission at the Westchester Division, he suddenly became worse, with additional signs of incontinence of urine and feces, and blatant evidence that he had been excessively indulging in alcohol. From the patient's wife, following his admission, it was learned that in the two preceding years he had suffered occasional blackouts, periods of amnesia; that two months prior to admission he had fallen heavily in his bathtub, sustaining a scalp wound in the occipital region, requiring three sutures; and that three weeks prior to admission he had been discovered in an unconscious state in his hotel room, which had not been reported to the physician in previous attendance. It was further stated that he had lapsed into coma for a short period while enroute to the Westchester Division. Immediate examination, following his admission to the Westchester Division, found the patient in a drowsy state but he could be easily aroused. He was disoriented in all spheres and was incontinent. On ophthalmoscopic examination, the left disc appeared normal but there was an early papilladema on the right, and the right pupil was larger than the left, but

both reacted to light. The deep reflexes were all more active on the left with positive left Hoffman, Babinski and Rossolimo reflexes and a positive Gordon on the right. There was a definite motor weakness of the left extremities and slight ptosis of the left eyelid. An electroencephalogram revealed marked, diffuse slowing, especially on the left side. An x-ray of the skull was negative. Neurological consultation reported confirmation of the initial neurological findings reported above and these were considered indicative of increased intracranial pressure with evidence of bilateral pyramidal tract involvement, but mainly on the left. The patient was referred to neurosurgery for further study, resulting in the localization of a chronic, subdural hematoma which was evacuated from the left parietal region. Two weeks subsequent to surgery the patient returned to the Westchester Division to undergo treatment for his problem with alcohol. On his return, he was well-oriented although somewhat dull and apathetic, with transient aphasia. He remained under treatment for four and a half months, during which time the residual neurological symptoms and signs satisfactorily cleared. A final electroencephalographic record indicated only slight residual abnormality in the left anterior temporal region.

Mentally, this patient presented symptoms which were not inconsistent with his prolonged over-indulgence in alcohol. However, the immediate and careful neurological survey indicated the presence of additional factors which led to the recognition and treatment of the subdural hematoma.

The need for alertness to the existence of any physical condition associated with presenting psychiatric symptoms is continually emphasized. The ability to recognize and to differentiate speedily neurological conditions masked by evidence of mental and emotional disturbance is apparent. The psychiatrist should always keep in mind, and continually rule out, neurological or organic etiologies in those psychiatric syndromes which seem to be typically functional, for only by maintaining a high index of suspicion regarding these conditions can errors be avoided which might lead to serious consequences. Furthermore, the psychiatrist should not ignore the treatment of the functional overlay of the organic disorder.

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TREATMENT OF TUBERCULOSIS OF BONE AND JOINT*

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IN PREPARING this paper I have been greatly disturbed by two factors. First, the possibility that the ideas proposed might prove wrong or be misinterpreted, and that blind acceptance might lead the unwary to disaster. Secondly, that since there is not a paucity but rather an overwhelming plethora of statistics and patient material upon which to draw, the selection for presentation might not be properly balanced, and not produce a reasonable perspective. I was greatly honored in 1950 in having the opportunity to present a lecture before The New York Academy of Medicine on *Tuberculosis of Bones and Joints*[1]. A review of this discourse would make an excellent introduction to the present subject. Only certain highlights from it can be touched upon in the present paper.

Before discussing treatment of bone and joint tuberculous lesions one must review, at least briefly, the pathological manifestations of such lesions. Otherwise one cannot understand the problems involved nor the rationale of treatment advised, particularly as to the duration of therapy.

BASIC PATHOLOGY

All such lesions must perforce be due to the presence of the Mycobacterium tuberculosis and its products with their effects on the tissues of the host. The presence of the organism in bone, joint or soft tissue is predicated upon the pre-existence of a tuberculous bacteremia emanating from a previous focus. It has been well established that such primary foci of infection usually exist either in the lungs or in the lymph nodes. Speculation in the individual case as to whether ingestion or inhalation was the mode of inoculation of the primary focus is

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not germane. The main fact to be held in mind is that bacteremia must have occurred and implantation of bacteria been widespread throughout the body of any patient having even a solitary bone or joint lesion. With such tuberculous bacteremia present one should not be surprised at the development of a solitary bone or joint lesion, nor indeed of multiple lesions. Instead, one wonders why overwhelming miliary involvement of all parts of the body does not take place at the same time in every case. If we could understand why only scattered instances of active disease result when there is multiple seeding we would know much more as to how to prevent the occurrence of the solitary lesion, and perhaps know more as to its control when once established. We make this observation at the beginning of this discourse to emphasize that, while our present knowledge seems considerable, we should humbly recognize that in reality we are taking painful step by painful step in our search for proficiency in the understanding and control of these lesions.

Granted the implantation of the bacteria in a single locale, we know that the bacteria and their toxins result in the formation of a tubercle with typical giant cells. This develops caseous necrosis in the center. The cell is finally destroyed and its focal necrotic structure becomes confluent with other similar microscopic lesions to form large caseous necrotic areas. Endarteritis and periarteritis develop, furthering the necrotic process. Denervation of the area is accomplished by perineural fibrotic changes, by compression of neural structures by the mass of caseous necrosis present and by actual destruction of nerves passing through the diseased area. Liquefaction of the caseous material may finally occur, and the fluid content of abscesses so formed be increased, due to the reaction of surrounding tissues irritated by the contiguous disease process. Stripping of the periosteum of osseous structures and stripping dissection along fascial planes occur, adding to the destructive action of the pathological process and causing further loss of blood supply and innervation. The appearance of calcification, which occurs in response to any degenerative process, of detachment of cartilagenous structures whose base is undermined by the process, of bony fragmentation where the process is slowly progressive, or apparent bony sclerosis where devascularization and stripping of periosteal structure are sudden and complete, can and does alter the clinical picture of the lesion and its appearance on x-ray films. Since any change in the roentgenographic

appearance depends upon a change in specific gravity of the osseous structure, or alteration of such structure by disruption of continuity either in minor detail (lysis) or gross extent (fragmentation), early delineation of an osseous lesion is impossible from the roentgenogram alone. The soft tissue changes accompanying bone involvement are much more indicative of the presence and extent of such lesions than the appearance of the osseous structures themselves.

It must be granted that *early* diagnosis of an osseous lesion is impossible; that when finally appreciated, it must be considered *late;* that the extent of the lesion is impossible to recognize clinically or roentgenographically. This is true whether the disease be of the spine, of the femur, the os calcis or elsewhere. Therefore, in considering treatment—and especially the duration of treatment—one must consider how long it may take to reverse tremendous pathological changes already present. Where only synovial changes are noted, one must be guarded as to the correctness of diagnosis. One must consider the possibility that the synovial reaction is due to underlying bony involvement, which may be much more extensive than suspected.

If we believe that we have discrete involvement of a single structure, we can classify tuberculous lesions in order of difficulty of treatment. The simplest to care for are those involving tendon sheaths, then synovium, then fascia, and finally osseous structure. This classification of the comparable seriousness of lesions is not based on tuberculous inflammatory changes present, but rather upon the known clinical results of control by our presently existing armamentarium of anti-tuberculous agents. There are those of us who can, in memory, return to the pre-surgical era of the treatment of orthopedic tuberculous lesions. Remembering that era, we would have to change the order of gravity of involvement of the structures named and perhaps be unable to assign any lesser import to one than the other. All were tuberculous lesions and all certainly often defeated one in securing either healing or a satisfactory reparative result.

Preventive Measures in Management

It would seem unnecessary to state that the prevention of occurrence of such lesions is greatly preferable to the healing and cure of them once they have occurred. One cannot, however, fail to emphasize this point. No practitioner of orthopedic surgery, whose experience

began later than 1945, can appreciate the change that has taken place. Only those whose remembrance goes back beyond 1920 can truly envisage the role of prevention. There was a time when great institutions were developed and functioned mainly for the care of such patients. The names Trudeau and Saranac Lake are still known but are fading. The New York Orthopaedic Dispensary and Hospital and the Hospital for Joint Diseases both had convalescent hospitals devoted mainly to the care of tuberculous orthopedic cases. Other similar institutions existed. They exist no longer. This is due to the decline in the incidence of this disease entity. The development of inspection, pasteurization and purification of food, milk, and water, the segregation of the seriously afflicted patient, the lessening of congested living conditions, have all played a role in this decline in incidence. Despite the beneficial results of such preventive measures (and they were great), a considerable residual pool of tuberculosis has continued to exist. From this pool of infected material, existing in a city of seven million people, a mass of material of these bone, joint, fascial and tendon sheath lesions was steadily accruing. Further preventive measures were necessary to reduce this total. There was a continuing incidence of primary lesions of tuberculosis of considerable size. In each thousand patients with a primary complex, a definite percentage of osseous and joint lesions would develop. Sea View Hospital and three other major municipal institutions for the tuberculous were still overwhelmed. Many tuberculous patients still had to be treated in the general hospitals of the city. Other preventive measures did develop, however. They were not looked upon at the time as preventive measures. In 1945 streptomycin came into general use. With this antibiotic, primary complexes were brought more rapidly under control. Not only did the number of active primary complex cases drop, but those that occurred were more rapidly resolved. At the same time there was a proportionately direct decrease in the incidence of orthopedic manifestations. In 1951, the nicotinic hydrazids came into use. Again, primary complexes were more rapidly aborted and healed. Again the percentage incidence of orthopedic lesions resulting from primary complex cases markedly decreased. The general practitioner began to use the isoniazid freely, finding it a potent weapon of therapy. Granted that tuberculosis may not have been present in many such cases, this medication surely should be considered as having served as a potent preventive agent in management. Whereas, before its use, the

patient population of institutions treating tuberculosis had already been greatly reduced, with the advent of the nicotinic hydrazids, many of these hospitals have had to close their doors for lack of patients. With regard to the decrease in the incidence of tuberculosis in general and to the occurrence of bone and joint lesions in particular, perhaps the best illustration of what has occurred since the advent of streptomycin, and later of the isonicotinic hydrazids, is the fact that of the four municipal hospitals for tuberculosis in the New York area only one now survives,—namely, Sea View. Seaton, Neponsit and Otisville are closed—only names now! Another example is the orthopedic service at Sea View Hospital itself, first as to reduction in number of patients and secondly as to mortality figures. Before 1945 there were 250 beds assigned to orthopedic lesions at Sea View. For admission there was a waiting period of six weeks and it was almost impossible to get a patient on to this waiting list. With the advent of streptomycin there were still 250 beds, but the waiting period, while still often six weeks long, was open, and frequently the patient could be admitted within three weeks. Since the advent of the nicotinic acid hydrazids the orthopedic service at Sea View Hospital has shrunk to only 75 beds. There is no waiting list. From time to time directives are issued to the other city general hospitals and any bone or joint cases on their wards are ordered sent to Sea View Hospital. If one reviews the mortality record at Sea View on the orthopedic service, other startling figures appear which confirm the improvements that have occurred. For the five year period before the advent of streptomycin, there were 19-21 deaths of orthopedic cases each year; following the advent of streptomycin, there were 7-9 deaths a year over a similar five year period. Following the advent of isonicotinic hydrazid, deaths have dropped to two or three a year and these occur in patients who have been admitted with an overwhelming infection in multiple joints, kidney, lungs and sinuses with mixed infection,—who are markedly debilitated and often practically moribund. Some of these deaths are due to cardiac or other conditions unrelated to tuberculosis. While some of the above results are due to prevention of disease and prevention of metastatic spread of disease, some, of course, are directly attributable to improved methods of treatment.

One cannot disregard the lessons learned in the past as to the treatment of such patients. The need for physical bed rest, non-weightbear-

ing support of involved joints, the extension of the principle of rest by adequate fusion of destroyed weightbearing joints, the maintenance of an optimum nutritional status of the patient, elimination of mental stress and worry incident to his usual contacts and problems, the ablation of diseased areas in part or in whole, the need of combined treament of the patient as a sick individual requiring the attention of many branches of medicine,—medical, surgical, neurological, gynecological, ophthalmological, dental, etc.—cannot be disregarded.

Bacterial Control

Discussion of the surgical management of the tuberculous patient will, for the present, be deferred. Great as its use was in the days before antibiotics or anti-tuberculous chemicals, it is now an adjuvant and its indications are quickly covered. Before we consider surgery, then, we would prefer to discuss bacterial control. Without such control, in the so-called surgical era, disastrous results occurred despite the best planned and best performed surgical procedures. Since control of the Mycobacterium tuberculosis, surgery has become tremendously effective and is followed by a markedly reduced morbidity and mortality. The results have been markedly improved with regard to development of deformities and ankylosis. Let us therefore continue on to a consideration of bacterial control.

Before considering the anti-tuberculous antibiotic and anti-tuberculous chemicals, we should briefly consider paramino salicylic acid (PAS). While the use of streptomycin became general in the United States in 1945, this antibiotic was almost impossible to obtain in the European area. Paramino salicylic acid was available in Europe. It is not well known that a commission was formed to visit Europe and to determine the efficacy of paramino salicylic acid. The report of this group, never widely distributed, was that though little effect could be seen from its use, it should not be discontinued since it was all that was available at that time in that area. Our experience with it on the Orthopedic Service at Sea View has been negative, both as to its effect on tuberculosis by itself or in combination with streptomycin. We believe that its use merely adds another source of toxicity to the patient. We have never seen the adverse effects of increased destructive activity due to the development of the resistance of the tuberculous organisms to streptomycin or to the nicotinic hydrazids. We investigated the resistance of

organisms on the prolonged use of streptomycin, and, although numerous instances of development of such resistance were noted, continued healing took place over a period of continuous medication, often for one, two and three years, even with resistance present. We saw, of course, instances in which healing did not occur. We never saw an instance in which fulminating infection reoccurred due to resistance of the organism to streptomycin. We saw no instances in which we believed the administration of PAS with streptomycin enhanced its value in orthopedic lesions. Our experiences have been reported on 355 consecutive cases of bone and joint involvement, and published in the *Journal of Bone and Joint Surgery*[2]. We do not use paramino salicylic acid.

The above are our opinions based on personal observation; they are not based on statistically valid data and must be considered with this in mind.

Streptomycin's effectiveness depends upon its ability to arrest the growth of the tubercle bacillus. With prolonged use we found that certain toxicities developed. Five per cent of the patients became totally deaf, 20 per cent showed demonstrable deafness of varying degree, 12 per cent developed severe gastroenteritis at some time during the period of medication, and 3 per cent developed exfoliative dermatitis. In most of these it had to be given by injection and over a considerable period of time. With its use, marked improvement over any previous form of treatment was gained. Sterilization of foci could not be depended upon. Surgery, as "in the surgical era", had to be continued. Weight-bearing joints required arthrodesis, if safety as to permanency of result was to be depended upon. It is certain that its use promoted a great advance in the care of these patients with bone and joint lesions. The main effect was to improve the general condition, to reduce the acute inflammatory nature of the disease, to control secondary invading organisms, and to maintain the patient in adequate general bodily condition until surgical eradication or arthrodesis could be done. Our talk before the Academy of Medicine in 1951 was concluded as follows: "As a matter of fact it is not impossible that in the near future some agent will be discovered so efficient as to practically wipe out tuberculosis. Then, perhaps, some newer generation may ask what were these lesions. . . .?" We did not then know of the tremendous advance in these conditions which would come about within a few short months.

Let us go on to a brief description of this treatment.

The nicotinic acid hydrazids became available at Sea View in 1951. They were first used by the Medical Service and showed such promise by the fall of that year that the other services began to employ them. Both the isoniazid (Rimifon), (Nydrazid) and the iproniazid (Marsilid), were in very short supply. By the fall of that year it was already appreciated that severe toxicities could result from the use of any of these. But these toxicities were much less severe when isoniazid was employed. Fortunately, for this reason the Medical Service released the iproniazid to the Orthopedic Service for trial. Six almost moribund patients were selected and treated with iproniazid. Of these six, five are still alive and four of them have completely recovered. Since that time a thorough investigation of iproniazid has been done. All toxicities were carefully evaluated and the benefits occurring were noted. All of the beneficial actions and many of the toxic actions have been translated for use in conditions other than bone and joint tuberculosis. Because of the tremendous benefits accruing, it was evident that the toxicities had to be understood and controlled and such was accomplished. Major forms of toxicities were recognized, principally those involving the central nervous system (psychosis) and the toxic effects on the liver (hepatitis). Throughout our experience we have never seen hepatitis as a toxic manifestation. Others have reported its occurrence. We have even used the drug when Laennec's cirrhosis was present, and without further liver damage. At first, a dosage of 4 mg. per Kg. of body weight per day was maintained. When this dosage was given for more than a six weeks' period, psychoses developed in approximately 10 per cent of the cases and in five instances these were of considerable severity. Such psychoses were of the euphoric type. On three occasions these required institutionalization for from three to six weeks. All recovered when the drug was discontinued. Many minor toxic symptoms occurred, including dryness of the mouth, constipation, twitching, lack of ocular accommodation, etc., approximately to the number of 20. These were noted to occur and disappear even with continued medication. Occasionally, lowering of the dosage or a temporary withdrawal of the drug, with later resumption at a lower dosage level, was necessary. When this occurred, there generally were personality changes suggestive of the early euphoric psychotic condition accompanying the minor toxic manifestations which forced the alteration of dosage. It was noted that

patients outside of the institution and in relatively normal home surroundings tolerated medication better, with less evidence of toxicity. Following the review of the first year's experience it was found that our maximum dosage had been reduced to 3 mg. per Kg. of body weight and a minimum dosage established of 2 mg. per Kg. At the present time, where severe disease exists, a patient is placed on 4 mg. per Kg. of body weight per day for two to four days and then the dosage reduced to 2 mg. per Kg. and continued at this level. Occasionally, medication must be discontinued for a few days and then restarted. At this level of dosage we rarely see personality changes, aside from mild euphoria, and no psychoses have developed.

Because of the toxicities developing with the use of iproniazid, cessation of manufacture was considered but, by agreement, a comparative study was run of two series of cases, each group with tuberculous bone and joint involvement, one treated with isoniazid and the other with iproniazid. On a basis of clinical estimation (which cannot be satisfactorily supported statistically), the iproniazid was 21 times as effective as isoniazid in the treatment of bone and joint tubercular lesions. This series of cases has been reported. I have seen no patients with permanent effects from toxicity, no deafness, no gastroenteritis, no exfoliative dermatitis. We have reported the results of treatment of patients with iproniazid and such results are recorded[3-9]. At the present time we use only iproniazid in the treatment of bone and joint tuberculosis at Sea View and St. Luke's Hospitals.

Surgery

Surgery must accompany the use of iproniazid. This does not mean that every case of bone and joint tuberculosis must be operated upon. When, then, will one use surgery? I believe that every tuberculous lesion of the spine needs a stabilizing spine fusion, despite the fact that it is probable that in some of them the diseased process could be arrested by iproniazid. However, during, or after arrest of the disease, further collapse of the involved bodies will occur. This can, to a great extent, be prevented by adequate spinal fusion.

In the adult, I believe that arthrodesis of any weightbearing joint which has been so badly destroyed by disease that salvage with function has been compromised, should be done. In children I believe that arthrodesis of involved badly destroyed weightbearing joints may have

to be done, but delay in decision is justified when the patient is on iproniazid therapy until demonstration of functional deformation or satisfactory result becomes evident. Certainly in children we have seen certain weightbearing joints with gross bony defects (particularly the knee) heal successfully to an extent we would not have believed possible. Except in the spine, where joint involvement has occurred without obvious bony destruction, iproniazid may cause arrest of disease and even cure, on occasion in the adult, and frequently in children, and this without surgery. The greatest indication for surgery in the tuberculous joint at the present time is for early and positive biopsy.

Dosage and Duration of Medication

We have spoken of dosage previously. We can accept as safe, a dosage of 2 mg. per Kg. of body weight per day, continuously administered over many months. We have one patient whom we have purposely kept on such dosage for over five years. No toxicities have developed. Many patients have been on medication for over two years. In a case of proved osseous tuberculosis the question arises as to how long should one continue medication? We do not know. Certainly, if one recalls to mind the basic pathology, the tremendous destruction which can take place without any possibility of demonstration or visualization by roentgenogram or otherwise, a prolonged period of time is required for sterilization and resolution of the lesion. In soft tissue lesions of tendon sheath and fascia, etc., I believe that treatment for six months to a year following the healing and subsidence of all inflammatory reaction is sufficient. In osseous lesions I believe that two or three years of medication, as a minimum, is required. The drug is relatively inexpensive, toxicities can be controlled, oral administration is simple. Patients can afford and can safely continue prolonged medication. Further time, further experience and further statistical data gained as the years go by may provide an answer as to the duration of treatment.

In the meantime, just as in 1950 we thought and hoped that a newer form of medication would become available to control these lesions, so we continue to hope. Even with the advance from conservative treatment of bone and joint tuberculosis to surgical management, to control with streptomycin and now to even better control

with iproniazid (Marsilid), there is still a residual percentage of failure in the treatment of such lesions. It is difficult for the younger group of physicians to realize and to appreciate the extent of the advances that have already been made, and the truly wonderful era in which we live. However, further improvement is desired, is to be expected and will be accomplished.

Grateful acknowledgement and thanks are extended to Doctors Alphonse Della Pietra, Howard Wright, William Fielding, Leon Katowicz and all our many past and present residents of Sea View Hospital, for their tireless and unselfish contribution of time and effort in the furtherance of our work in this field.

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MANAGEMENT OF SOLITARY THYROID NODULE

*Transcription of a Panel Meeting on Therapeutics**

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MODERATOR LAWRENCE W. SLOAN: This subject, *The Management of the Solitary Thyroid Nodule*, has, conventionally, been largely a matter for surgeons. In general, we have thought of dealing with nodular goiter by surgical means on the assumption that these goiters carry the implication of malignancy, and since the conventional treatment of malignancy has been by surgery it has been customary to handle nodular goiters, particularly solitary nodules of the thyroid, in that manner. However, there are differences of opinion on almost every aspect of the subject of thyroid cancer, and this one is no exception.

If surgery is not the method of choice, what *is* the method of choice and why? Should surgery be combined with other methods of treatment? If so, under what circumstances? If surgery alone is to be used, the question then arises: When should surgery be used and how?

As a basis for our discussion it seemed to me that it was advisable for each of the panelists to state a point of view, to present in essence the experience each has had with this problem in his own field as it relates to the management of the thyroid nodule. The pathologist (who has thrown much light on the subject, but who has also done his share of throwing it into a state of confusion), should clarify some basic points on what is meant by the solitary nodule; what do solitary nodules turn out to be; is there any validity to the assumption that a high proportion of solitary nodules are cancers; does this hold true for all age groups? These, and perhaps some other questions that might occur to me and to you, I shall ask Dr. Frantz to answer in a statement now.

DR. VIRGINIA KNEELAND FRANTZ: The subject assigned to me by Dr. Sloan is, "The pathologist looks at the problem." I think it should have been extended to say "and shivers with fright", because the responsibility of differential diagnosis is really a hard one to take. When the disease is locally, clinically aggressive or shows evidence of distant spread, obviously it is easy for the surgical pathologist to make a diagnosis.

We are concerned today with a patient who shows no signs of hyperthyroidism, and who has what is thought to be a single asymptomatic nodule, a lump in the thyroid gland. Standing beside the operating table through the years since 1924, having first been allowed to examine the patient clinically, I have seen the single nodule turn out to be multiple, and multiple nodularity turn out to be an adenoma in one

lobe and so-called "thyroiditis" in the other. In our experience malignant disease is more apt to be found when the nodule is thought to be single on physical examination and turns out to be single at the operating table. Ten years ago Ward pointed out that, in his experience, if thyroid cancer was clinically evident before operation, 80 per cent of the patients would be dead within five years; if it was demonstrated at the operating table, the per cent dropped to 60 per cent; and if it was made on histological study, only 20 per cent were dead at five years. This is the reason for the shivers of fright of the surgical pathologist.

If the surgeon hands the surgical pathologist what he thinks is a benign lesion, and the surgical pathologist considers it histologically malignant, and makes the diagnosis of papillary carcinoma or of malignant adenoma, in many large thyroid clinics that diagnosis now leads to further radical surgery which means, at best, a permanently athyreotic patient who has to be maintained for the rest of her or his life on substitution therapy. There are, of course, other hazards of surgery.

(Slide) I would like to show you the breakdown of 177 odd cases, cases which have a possible ten year follow-up. These break down into Grade I which may be either papillary or follicular, 78 malignant papillary adenomas or adenocarcinomas, and 60 malignant adenomas or malignant follicular tumors. So it is seen that 44 per cent of our carcinomas are papillary, or predominantly papillary, and 40 per cent are follicular. The latter correspond to the so-called "benign metastasizing colloid goiter". The other grades are those which are supposed to be more malignant. As a matter of fact, Grade III contains the only ones I really recognize as highly malignant; Grade II comprises those that "I don't know what they are", and most of those eventually fall into Grade I. They have peculiar histological patterns for which no single pathologist has had enough experience to make sure of the prognosis. A ten year follow-up is not really long enough to make a prognosis because in these first two types in Grade I, the papillary carcinoma and the malignant adenoma, the history is very long and they are of very low grade malignancy. However, of those patients with papillaries, a third are already dead in this group, not all of disease of course, and of those with malignant adenomas, about 40 per cent are dead.

Now I should like to show you just what my particular problem is, any pathologist's problem, in the great variety of appearances of these

tumors at the operating table.

(Slide) This is the tumor of a patient who was 29 years old in 1928, who for five years had had a mass in her gland. She had an incomplete operation because in those days we did not believe total thyroidectomies for carcinoma were necessary. Sixteen years later this nodule was removed from in front of the sternocleidomastoid muscle. It is a cystic tumor with a papillary projection in the cystic cavity. She had another recurrence very recently and was again operated upon. Again the tumor looked relatively benign. She has never had any metastases. She is now athyreotic. So she is still alive 27 years after operation and 30-odd years after the onset of her tumor. The question is: Is this a pathologist's cancer or a patient's cancer? Is this an implant or is it a spread of disease?

(Slide) The next picture is that of a man of 26 with cervical node metastases who was operated on and had a somewhat more fibrotic papillary tumor, and is now well, 16 years after radical surgery.

(Slide) This shows a patient who presents a few months' history of a lump in the lateral neck. This is easy for the pathologist. A biopsy is done and it shows papillary cancer, and we can see now, after radical surgery, what the extent of her metastatic disease was; but when the lobe was removed, that little, tiny nubbin in the upper pole of the bisected gland on the right side, which was not palpable clinically, is the occult primary.

These are the varieties of gross appearances that these tumors, the papillary ones, can give. The malignant adenomas are sometimes just as difficult to find as far as the primary is concerned.

(Slide) Here is a woman who ten years ago had a pain in her back. Later she had difficulty in moving her legs. She was operated on, and this well differentiated thyroid tissue was removed from her spine. It was, of course, a malignant follicular tumor, but it looks like relatively normal thyroid. Then her gland was palpated by a number of eager observers and only one thought he could feel it. I doubted whether he could, but at least he guessed the most common site for the tumor. Here it is. It was a little over a centimeter in diameter. This is the front half of the gland which was removed by total thyroidectomy bisected and that little pale place there is the small 1.5 centimeter calcified tumor deep in the lower portion of the right lobe.

(Slide) She is well today, ten years after onset of symptoms from

her metastasis, having been treated by both x-ray and radioiodine. Her metastasis was treated with radioiodine after the limit of x-ray treatment had been reached.

From studying these cases since 1924 with Dr. Sloan and with the other surgeons of the Thyroid Clinic as well as with Dr. Werner, this is what I think I have learned:

1. That thyroid carcinoma, perhaps particularly the papillary type, can be implanted. We therefore advise against open biopsy of the single nodule but do advise a lobectomy as the biopsy specimen. If the nodule is benign, the patient still has the contralateral lobe for maintenance of euthyroid state.

2. I think I have also learned that proven cancers may have a soft as well as a hard primary tumor and that clinical and gross examination can be misleading.

3. That prognosis can be guessed, perhaps, by the histological type but that there are many surprises. The extent of disease and the duration of disease, which are correlated with the age of the patient, are far more important than the histopathological type of a Grade I tumor, which is the one we are really concerned with today.

4. That very small primaries may have widespread metastases, and that the asymptomatic nodule, if we are fortunate enough to feel it, should therefore come out, if possible before metastases have taken place. Unfortunately, there is ample evidence that metastases can occur early and remain cryptic for a long time. This is documented when we see unexpected distant metastases at the termination of disease with no return of the local tumor. This indicates, therefore, that surgery has been effective for the primary lesion.

5. That it is easy in hindsight to recognize a malignant tumor but hard when it is circumscribed local disease. If a nodule is removed, and there is no recurrence after 20 years, the clinicians usually exclaim that the pathologists were "overdiagnosing"—a hideous modern misnomer for making a mistake. But we cannot put the clock back 20 years. We cannot put the controversial nodule back in the neck and see what would have happened if the surgeon had not removed it. Even the most medically minded of our medical colleagues have to admit that sometimes a patient is cured of a malignant tumor because it has been removed in time. These are the so-called "pathologists' cancers" because they have not killed the patient, but without surgery they

might well have become "patients' cancers". Personally, I like to play safe, referring the patient to a competent surgeon. In competent hands before the invasive stage of disease, our figures show that thyroidectomy has a pretty insignificant morbidity and mortality.

MODERATOR SLOAN: *Dr. Frantz, before going on, may I ask one question? What do other solitary nodules turn out to be, besides cancer?*

DR. FRANTZ: They turn out to be adenomas, in which we can find no histological evidence of malignancy; that is to say, no invasion of the capsule, and no blood vessel invasion. They sometimes, but rarely, are cysts. That occurs more often, I believe, in Italy than in the United States. But for the most part a true solitary nodule, so proven at the operating table, not by the physical examination, is an adenoma. That is the differential diagnosis that is so difficult. If we call it benign, nothing more is done; if we call it malignant, the rest of the gland usually comes out. Histological differentiation is not as easy as some people think.

MODERATOR SLOAN: Then I, too, would say, perhaps that there are some cases of simple non-toxic nodular goiters in which there are solitary nodules.

Is there any real validity to the assumption that a high proportion of these are cancers?

DR. FRANTZ: You ask, are they cancers from the start instead of adenomas in which malignant degeneration occurs?

MODERATOR SLOAN: Yes.

DR. FRANTZ: I believe the ones that turn out to be malignant in the end are potentially malignant from the start.

MODERATOR SLOAN: I think in a discussion of this sort we should keep in mind that we are not aiming primarily at evaluating results of surgery which, as I said, has been the conventional method of treatment. What we are trying to determine are the principal features of the behavior of the disease. For, as most people who know about thyroid cancer and thyroid disease in general realize, the natural history of the disease is very long and, therefore, the results as they have been tabulated and published in many places are not comparable. They are not a sure basis for deciding which method of therapy is right, whereas if we know something about the nature of the goiters, something of their characteristics and behavior, particularly of the solitary nodules, we can base our therapy much more soundly upon that information

than we can upon the statistics of surgical therapy alone.

To some, it seems odd that a surgeon should advocate a method of management of a conventional, surgical lesion, such as a nodular goiter, by other than surgical measures. I have asked Dr. Crile to present his data on regression of thyroid nodules, especially cancer, under thyroid administration, his operative approach to glands he thinks may be cancerous, the basis for this and for subsequent treatment of those glands found to have cancers.

I shall ask Dr. Crile to answer the question, when is the surgeon not a surgeon and why?

DR. GEORGE CRILE, JR.: I think I could very well take as my text one of the last remarks made by Dr. Frantz,—which, if I did not write it down incorrectly, reads, "If we call it malignant, the rest of the gland usually comes out", and on this basis I think one can readily interpret the difference in the results which have been obtained in these low grade tumors in our experience in Cleveland and here in New York, where the mortality rate seems to be considerably higher in this group.

This sounds like a rather sweeping statement to begin with, but it is well based on physiology. Hitherto, and up until the last five years or so, the question in our mind had always been, first of all, is this a nodule; and second, what is the best way to take it out? These are anatomic questions. Now we ask ourselves, why is this nodule present, and how can its further growth be prevented? In other words, we have basically switched from the anatomic to the physiologic approach in the management of thyroid nodules.

This is quite in keeping with the development of the known basic scientific work which has been done throughout the world, by Furth and Foulds, Bilshowsky, Purvis and others. These investigators have proven that there are literally dozens of different types of cancers occurring in endocrine glands which can be produced at will in experimental animals by producing an imbalance in the endocrine environment of that animal. They have shown that these tumors go through phases of hyperplasia, then adenoma formation, and then the formation of what is known as a dependent cancer—a cancer which can live only in the presence of the disturbed endocrine environment which produced that cancer initially. Finally, with the persistence of that disturbed environment, some of these cancers become autonomous and independent, and on transplantation, can grow even in normal animals.

The classic experiment along this line is that of Purvis, because he was working with the thyroid. Here we have a simple endocrine axis: the pituitary-thyroid axis—I am sure you are all familiar with it, but to refresh your memory [sketching on blackboard] there is the pituitary, there is the thyroid, there is the thyroid stimulating hormone in the pituitary and the thyroid hormone acting in a feedback just like a thermostat, so that when this is increased, this is suppressed, and vice versa. On that basic principle, cancers can be produced at will in the thyroid of experimental animals by blocking the output of thyroid hormone and raising the level of the circulating thyroid stimulating hormone of the pituitary. This can be done in animals and can be specifically prevented in those animals by the administration of thyroid. The way it can be done is by the administration of thiouracil over a long period of time, which blocks the thyroid function and increases TSH, and exposes the thyroid to an environment, chemical environment, saturated in TSH, the specific growth hormone for the thyroid. In other words, cancer, an abnormal growth, results from overstimulation by the specific hormone. Or, if that is not the basic cause, it is at least a promoting agent without which that cancer does not develop because specific protection against the development of this cancer can be given by the administration of an adequate amount of thyroid hormone, which, of course, immediately suppresses the output of TSH from the pituitary gland. The thyroid gland first undergoes hypertrophy and hyperplasia, then adenomas form, then dependent cancers, which cannot be transplanted into normal animals and which will not even be maintained unless the animal remains on thiouracil. These dependent tumors will atrophy, if the animal's thyroid balance is restored and the pituitary hormone suppressed. But finally, with long continued thyroid stimulation by TSH, autonomous and highly malignant undifferentiated cancers develop, and nothing stops these. Interestingly enough, however, some undifferentiated thyroid cancers when taken out of this endocrine environment and placed into guinea pigs' eyes will differentiate back the other way, so even these cancers are under chemical control to a certain extent.

We have been much interested in applying these basic principles clinically. That is why we have done our level best to avoid, in treatment of low grade thyroid cancers, anything which runs the risk of inducing hypothyroidism and specifically stimulating the cancer to

growth. We have avoided total thyroidectomy unless it is going to be completely corrected by giving a minimum of 3 gr. of desiccated thyroid a day, indefinitely for the duration of life. We have avoided all attempts to treat patients with radioactive iodine, which also destroys thyroid function, unless we promptly correct the thyroid imbalance which ensues. We have avoided prolonged attempts to induce hypothyroidism by giving thiouracil to change the thyroid cancer from a tumor which will not take up radioactive iodine to one that will, because we know that in the long run prolonged hypothyroidism does not have that effect. It has the same effect that it does in mice and rats. It takes the thyroid cancer which is fairly differentiated, and which perhaps has some function, and ultimately converts it into a more and more undifferentiated cancer, which finally loses not only function but dependency upon thyroid hormone, and then becomes autonomous, undifferentiated, and a highly fatal disease.

Now before going further, I should like to show you clinical examples of some of the things about which I have been talking. We have observed some 40 patients with inoperable thyroid cancer or metastatic thyroid cancer, whom we have treated wtih desiccated thyroid during the past eight years. There is nothing new about this. This was done and reported by Dr. Thomas Dunhill back in the 1930's. Personal communications with Dunhill show that he has five patients whom he has now followed for 8 to 20 years. Each of the five had demonstrable metastatic or persistent local disease, two of them with pulmonary metastases which vanished and have not reappeared after periods of 8 to 20 years. This resulted solely from thyroid feeding.

Our experience has been identical. Our longest complete suppression —and not only suppression but vanishing—of thyroid metastases is now eight years, with another almost seven years. Some of these patients present a mixed history because small doses of radioactive iodine may have been given at some time. In all the cases which I shall show you, a sufficient interval of time elapsed, several months between the last futile attempt to make these patients take up radioactive iodine and the time the x-rays which I will show were taken.

We have 18 papillary carcinomas in this group. Only two of these failed to be arrested or to show marked regression in response to thyroid feeding. Of the so-called anti-invasive carcinomas, malignant adenomas, that Dr. Frantz discussed, we have about a fifty-fifty break.

About 50 per cent of them seem to respond. The more malignant cancers show no flicker of response and the same is true of the highly undifferentiated cancers.

(Slide) Just to show the sensitivity of thyroid tumors—and this is a patient with struma lymphomatosa—I wish to show the rather striking regression which occurs in benign diseases in response to thyroid feeding. This is about a year interval, thyroid having been fed in the meantime.

(Slide) This is an example of the regression of a metastatic tumor of the thyroid which was primarily papillary. Parenchymal metastases have disappeared, the interval being about six months.

(Slide) This is an example of the opposite effect in a young boy, normal chest at this point. Metastases developed three months after total thyroidectomy.

(Slide) This is the result of hypothyroidism induced by thyroidectomy and treatment with I^{131}.

(Slide) This is another, a few months later, after attempts with radioactive iodine and thiouracil, showing steady progress of the disease with complete filling of the chest and the child so decompensated, cyanotic and dyspneic that he could not tolerate full doses of thyroid. Without decompensation he had to be myxedematous in order to be alive. We have been able to arrest partially this growth for about a year. I think it is spreading slightly because we cannot keep him on full maintenance levels and have him survive, but now, about a year since this picture was taken, it is partially arrested.

(Slide) Another example, the best documented of all. At another hospital this girl was diagnosed as having sarcoidosis. Three months before this, her first chest x-ray was taken. No change was noted between the taking of the film and the taking of a lung biopsy on admission. Of course papillary carcinoma of the thyroid was found, not sarcoidosis. She was then placed on radioactive iodine; a total thyroidectomy was done, and a rather rapid spread followed.

(Slide) When the same patient was taken off radioactive iodine and given thyroid in doses of 3 gr. daily, her lungs cleared to this degree within a period of three months.

(Slide) Another example of the same thing. Notice the dates, a four month interval, total thyroidectomy and radioactive iodine in a young boy.

(Slide) Another clearing after thyroid feeding!

(Slide) This patient gave the following history over a seven-year period. Initially, he had had a tumor in the neck for about ten years. Enlargement was very slow, if any. When he was hospitalized for another ailment, the tumor was found and a decision made to remove it. However, it was only partially removed. It was widely implanted through the neck, as they usually are under such circumstances, and, within a period of six months, the patient developed a recurrence for which he was reoperated. All visible tumor was removed at this time and the present recurrence appeared only four months following the second operation. It can be seen that the neck is practically filled, is ulcerated and bleeding and this despite the fact that radioactive iodine had been given the patient in the meantime.

(Slide) We believed we could remove the major portion of the infected lesion, and, when indicated, we do not hesitate to do the most radical type of neck dissection possible in these low grade tumors. In spite of this dissection, which took all of the skin and all of the vessels except the carotid, with not a muscle except the posterior layer, we cut across tumor in several places where it was infiltrating the esophagus, continuing on into the base of the skull. We then placed him on thyroid.

(Slide) A year later he showed no evidence of recurrence. Now one tiny nodule has developed from which we excised an implant in the scar. It was no larger than a B-B shot, and that is the only growth-energy that this tumor has shown under desiccated thyroid.

I should like to say then, that we must consider these tumors as endocrine dependent. We must apply basic physiology, and I believe that one can recognize clinically 80 per cent of all thyroid cancers if one has had any training whatsoever in this field. In the first place, 20 per cent of them are highly undifferentiated, and anybody can make the diagnosis; secondly, about 10 per cent are of the middle range angio-invasive type, in about one half of which the diagnosis can be made from the history of the tumor, by the presence of metastases, and so forth. Then there are at least about 70 per cent in our clinic that are papillary carcinomas. About 40 per cent of this 70 per cent will have lateral cervical metastases present and demonstrable at the time that the patient is first seen. In fact, in nearly 50 per cent that is the dominant sign of the disease. It does not take a mathematician to add that up and show that 80 per cent should not be missed with any degree

of regularity in this group of thyroid cancers. Most of them can be recognized. Those which are recognized should be operated upon until we know more about endocrine control. In my opinion, the primary treatment of asymptomatic small thyroid nodules is the suppression of the thyroid stimulating hormone by desiccated thyroid.

MODERATOR SLOAN: I know there will be questions about this with further discussion of this point.

The internist investigating the thyroid also has an interest in the problem, and we would like to have his views about what investigations of mechanisms of thyroid function have to offer as a basis or approach to the management of the solitary thyroid nodule. What evidence is there, for or against, the assumption that some thyroid nodules are hormone dependent; which, if any, are hormone dependent; is there any discrepancy between the theory of hormone dependence and its actual occurrence? I would like Dr. Sidney C. Werner to tell us about some of the experimental work that he has done in laboratory and clinical investigation, which bears on these points.

DR. SIDNEY C. WERNER: Actually, I had planned to speak a little tangentially to the subjects that Dr. Sloan proposed, and I wonder whether I should try to go directly into what you have just asked me or proceed to speak about what I had originally intended.

MODERATOR SLOAN: Perhaps you can answer some of these questions when we come to the question and answer period.

DR. WERNER: The reason I departed a little from Dr. Sloan's plan was to stress the fact that the problem we are discussing originates with the internist. He is the one who first sees the patient. In the course of his routine physical examination, or in the course of examining a patient who presents with a known thyroid problem, he has to make certain observations. The first important requirement, therefore, is that the internist must have a technique of physical examination which is adequate for the purpose. After watching many people, I think an adequate technique of examination of the gland is not commonly possessed. Hence the first point I would urge is that one be able, particularly by displacing the gland, to examine properly for these thyroid nodules.

Once the nodule is discovered, the problem from the standpoint of physical examination is to know whether there is truly a single nodule or a mass of nodules; or, if there is a single nodule, whether it repre-

sents a non-toxic nodule, an adenoma, a cancer, or, as often happens, chronic thyroiditis. The pyramidal lobe of the gland or a recurrence in the previously operated patient of normal tissue versus a recurrence of cancer tissue may also be part of the differential diagnosis. These problems have to be approached in part from experience with palpation and in part from the use of the laboratory in order to appraise the function of the thyroid.

If the patient is hypothyroid, it is unlikely that a cancer is present. Usually, cancer does not invade so much of the gland that it produces overt myxedema. If the gland is hyperfunctioning, again it is unlikely that the nodule is malignant because the incidence of cancer in toxic nodules is not much greater than the incidence in toxic diffuse glands, and certainly does not approach the incidence of cancer in the non-toxic nodule.

Further studies may help in ruling out thyroiditis. As Skillern has shown at the Cleveland Clinic, and as Owen and Roberts, at the Mayo Clinic, have shown, one may give thyrotropic hormone diagnostically to people with chronic thyroiditis. They do not respond either by an increase in uptake or by an increase in the serum precipitable iodine level in the blood. Thus, a failure to respond in either of these two parameters is already suggestive that one is not dealing with non-toxic nodular goiter or cancer, but more likely with chronic thyroiditis. By determining the presence of a true circulating iodoprotein in the serum, one can then confirm the diagnosis of chronic thyroiditis.

By other techniques, one can establish whether a nodule in question is active or inactive, that is, "cold". By the administration of triiodothyronine, about one out of four patients with nodular goiter fails to show suppression of I^{131} uptake, whereas in the normal individual, three out of four people with non-toxic nodular goiter and the patients with thyroid cancer do show a rather striking suppression of uptake.

Another way of tackling the problem is by the scanning procedure. In this, one labels the gland with I^{131} and then runs a mechanical scanner across the neck to determine whether a nodule is either taking up a large amount of I^{131} or very little. I think this is often a tricky procedure because there may be a mass of active parenchymatous tissue behind a "cold" nodule giving a false impression of an active nodule. Contrariwise, there may be a nodule which is quite active bordering on a "cold" nodule. This latter could then not show up in the scinti-

gram. In summary, of these various methods, perhaps the most useful are the serum idoine, the uptake itself, and the two measures first mentioned, to appraise the activity of the nodule.

I believe we have not yet reached a point where one can anticipate the answer as to whether a tumor is able to sustain itself without hormonal stimulus or is dependent on a particular secretion without a trial of therapy. As can be seen, this is a controversial subject, with many opinions pro and con. One has to decide whether one can go the whole hog and follow Dr. Crile's lead—and certainly his results are impressive—or whether one should be guided by the experience with patients who have died in the face of therapy, or with nodules which don't disappear with treatment. In our own use of thyroid, in a series which must number about 150 patients with various types of goiter, there is no question that the non-toxic diffuse gland will melt away. As Dr. Crile has shown, patients with chronic thyroiditis usually also do quite well. Recurrences in normal tissue after surgery generally disappear with therapy. But in nodular goiter, one obtains a relatively small percentage with disappearance of the nodule subsequent to therapy. Does this mean, then, that these nodules are not hormonally dependent? Does it mean that there is underlying carcinoma?

The answer must come from more detailed investigation. One approach has already been made at our hospital, namely, to give thyroid to patients with thyroid nodules for a limited period of time. Various tests are first made to try to establish the nature of the underlying disease. One can see—and I think without risk, in view of the slow life history of progression of cancers of the Grade I variety—one can see clinically whether there is or is not a response to the administration of thyroid within this period of three months. Then we plan to remove these nodules, study them radioactively, pathologically, and so on, to see if some criteria can be found by which one can predict failure or success from treatment.

I, personally, don't believe we shall be able to find the answer. On the other hand, I think studies of this nature have to be made on a wide scale, and of course the results carefully analyzed. The physician who is not involved in academic pursuits can also justifiably try thyroid in nodular goiter for a limited period, I think. In the present stage of knowledge, however, he should set a definite time limit to treatment, and if there is not a dramatic result within this time, I think surgery

should be advised.

MODERATOR SLOAN: Proceeding with this type of investigation into the problem, I should like to ask Dr. Rulon W. Rawson what is known about the physiology of thyroid cancer, experimentally and otherwise, which will help us to decide the best method of management of the solitary or indeed the non-solitary nodules which turn out to be thyroid cancer.

DR. RULON W. RAWSON: This is a very stimulating discussion which is healthy because we are beginning to look at possible mechanisms. By examining such mechanisms we may come up with more physiologic means of treating some of these cancers.

Cancer of the thyroid is one of the more uncommon cancers but it is a unique tumor which provides unusual opportunities for study. Dr. Frantz has discussed the prolonged course run by this tumor. Studies going on all over the world suggest that at least some cancers of the thyroid are capable of responding to physiologic stimuli. Many of these studies, as Dr. Crile indicated, would suggest that the development of many thyroid tumors is a natural sequence to prolonged growth stimulation of the thyroid.

(Slide) We have produced a variety of tumors in the thyroids of rats treated with thiouracil. Here is the classic type of hyperplasia observed in the rat after two weeks of treatment with thiouracil. After three or four months we begin to see some tumors. Here is one, a rather solid tumor. It is an intrafollicular growth with a trabecular type of structure. Most of the tumors are of this type, suggesting a papillary and follicular structure. If the animals are carried on the drug long enough we see primarily a picture of involution. I suspect that this structure is a state of exhaustion. The thyroid is incapable of responding.

(Slide) It is interesting that some of these tumors which develop after prolonged treatment with thiouracil, disappear upon withdrawal of the drug. Here, however, we see how the hyperplasia has involuted but the tumor persisted for ten months after stopping treatment with the thiouracil. We might suggest then, that at least some of these tumors are in part dependent upon thyrotropic hormone of the pituitary for their development. However, withdrawal of the stimulus does not necessarily result in regression of the tumor. In the strain of animals that we have used we have seen no metastatic lesions. We have seen

no tumors that were transplantable unless a carcinogen was given along with the thiouracil. We have, however, the observations made at the National Cancer Institute to the effect that mice of a low tumor strain developed benign tumors of the thyroid on treatment with thiouracil, whereas mice of a high tumor strain treated with thiouracil developed metastasizing and transplantable tumors. There seems to be some endogenous factor which influences malignancy or benignancy of these tumors.

Functional studies that have been done on cancers of thyroid in humans in the last 15 years or more would indicate that, by and large, most cancers do not concentrate radioactive iodine. About 40 to 45 per cent will concentrate a measurable amount but it is only a small fraction of that collected by normal thyroid tissue. This can, however, be altered by subjecting the organism to certain physiologic stresses.

(Slide) Here we have observations made on a patient with metastatic carcinoma of the thyroid to the lungs. The thyroid was destroyed with radioactive iodine, after which he excreted most of the radioactive iodine. About six months later he was excreting only about 30 to 40 per cent of the radioactive iodine. He was placed on thiouracil for some time, after which he excreted only about 5 to 10 per cent of a test dose. He received a therapeutic dose and continued to excrete most of the radioactive iodine for well over a year, when he was again placed on thiouracil. Here we see that thyroidectomy and prolonged treatment with thiouracil increased the avidity of the tumor for radioactive iodine. Thyroidectomy has increased the function of metastases in about 50 per cent of over 50 cases that we have studied. We have also observed that the administration of thiouracil, which not only interferes with the metabolism of iodine but also augments the action of administered thyrotropic hormone, at least in experimental animals, causes this increase in function, which sometimes is maximal in about 65 per cent of the patients whom we have studied.

(Slide) Here we see an example of how thyrotropic hormone also stimulates the capacity of metastases to trap radioactive iodine. It appears that these tumors, when they do acquire function, are capable of producing thyroxine and triiodothyronine; at least we have been able to identify these hormones in the sera of patients whose metastases had acquired function and whose normal thyroids had either been removed or destroyed with radioactive iodine. It has also been demonstrated

that some patients whose only thyroid tissue is metastatic thyroid cancer, on receiving large doses of radioactive iodine, release thyroglobulin. This thyroglobulin, as we have studied it, is identical to that which has been recovered from normal thyroids. We might postulate then that the thyroid cancer can acquire all of the functions of the normal thyroid as the result of removal of the normal thyroid or as the result of the administration of thyrotropic hormone or an agent which augments the action of the thyrotropic hormone.

However, we have observed that more than half of the patients we have studied in the last three years have put out an iodinated protein which behaves differently on zone electrophoresis than does thyroxine or thyroglobulin. The major difference is that it travels with the albumin. This has been separated and has been proved not to be iodinated albumin.

It has been demonstrated that this compound has a molecular weight of about 60,000, and on enzymatic hydrolysis it releases monoiodotyrosine primarily, and possibly thyroxine or probably 3:3' diiodothyronine which, in the systems we have used, behaves like thyroxine. This compound is not found in normal serum nor found in normal thyroid tissue.

We would suggest that these observations mean that the malignant or the cancerous tissue of the thyroid metabolizes iodine by some other system than does normal thyroid tissue or that it breaks down thyroglobulin by some other enzymatic system than does normal thyroid tissue. Whether or not these abnormalities of function and growth can be reversed by the removal or the suppression of the thyroid stimulating hormone, I do not think is clear as yet. The first patients whose thyroid cancers I attempted to influence by the administration of thyroid hormone came into the old Huntington Hospital in 1938 and 1939. They were two patients, both 19 year old girls with papillary cancers. The first girl had a lesion which presumably was operable. The surgeon went into the mediastinum, but was thought not to have removed all the diseased tissue. She was treated later by x-ray, and then with large doses of desiccated thyroid, which she is still taking. She is doing very well. The second girl arrived at the hospital a few months too late, and the disease was not operable. She, too, received x-radiation and the same amount of thyroid hormone. She is still doing well. I would be reluctant to attribute survival of these girls until today to the treatment with thyroid hormone. Both had x-radiation; and this is oftentimes the natural

history of this disease especially in girls of this age.

We have seen rather dramatic results in a few patients with metastatic cancer of the thyroid to whom we have given thyroid hormone in rather generous doses. These patients also had had x-radiation before treatment.

We have also observed some patients with papillary cancers and with follicular cancers of the thyroid whose tumors have grown notwithstanding the fact that they were taking large doses of one of the thyroid hormones.

I would have to differ with Dr. Crile in his interpretation of this fine balance between the pituitary and the thyroid. I don't think it is nearly as sensitive a thermostat as I like to have in my house in this kind of weather!

(Slide) Here I have some observations made in rats receiving thiouracil for some period of time and then treated with thyroxine. After about two weeks of treatment with thyroxine, you will note that with the dose of 1.25 micrograms daily of L-thyroxine there was no effect on the uptake of radioactive iodine nor on the thyroid growth; that 2.5 micrograms daily did not have a suppressive effect on either the uptake or the thyroid weight; but that 5 micrograms a day did bring it back to normal; that the administration of 100 gamma a day of thyroxine, yes, did suppress the uptake of iodine to a very low level but did not make the thyroid as small as one would expect it to be had the pituitary been removed. D-thyroxine here seemed to be about one-tenth as active as L-thyroxine in such studies.

We have also attempted to suppress experimental tumors which had been induced by the administration of thiouracil, by administering thyroid hormones both as thyroglobulin and as thyroxine. Our results have been quite disappointing. We have not been able to make these tumors disappear from the thyroids of rats. It is possible we did not give enough thyroid hormone.

I think that, notwithstanding some of these differences in philosophy and in interpretation, it is very important to regard this type of study with open minds. I hope that definitive studies can be pursued in clarifying this particular question. It certainly would be most desirable to determine the effects of surgical hypophysectomy on the growing of all types of metastatic cancer of the thyroid in humans.

It is of interest that Dr. Sonenberg has been able to alter the thyrotropic hormone and produce a preparation which is not only inactivated

but capable of inhibiting the action of administered thyrotropic hormone in the experimental animals. Dr. Sonenberg is now studying this agent for its effect on the growth of human thyroids.

It is possible that some of the analogues of thyroxine which have little effect on the basal metabolic rate but considerable effect in preventing the development of goiters may prove to have more effect on the growth of thyroid cancers than the thyroid hormones now available. For example, one compound, triiodothyropropionic acid, is very intriguing. Its effect on oxygen consumption in rats and humans is about 10 per cent of that of thyroxine, whereas its ability to prevent the development of a goiter in an animal receiving thiouracil is almost equivalent of that of thyroxine. It is conceivable that with this differentiation one can administer large enough doses of a thyroid hormone so that one might really pursue Dr. Crile's theory to its ultimate conclusion.

MODERATOR SLOAN: This, as you can readily see, is a most interesting and provocative subject, and, as Dr. Rawson has pointed out, there are some data from the experimental field that make us wonder if the relationship between the thyroid and the pituitary in regard to the control of thyroid cancer is as simple a relationship as has been indicated.

I should like to say a word about our experience from a clinical point of view in this respect. For the past five years it has generally been our custom, in treating thyroid cancer, to do a total thyroidectomy as a first stage. We have, as it has turned out, staged many of these procedures, and then, because the patient was hypothyroid as the result of a total thyroidectomy, desiccated thyroid was given in about as large a dose as could be tolerated. This group of patients has subsequently had mediastinal or neck dissections. When mediastinal dissection is indicated it has been carried out because we believed that the progress of growth, the spread of the disease, was in the direction of the mediastinum, and although we were not certain that any cancer was there, we felt that the mediastinal dissection was the logical procedure to carry out. Of 14 of these patients who were on thyroid medication after total thyroidectomy we found that 10 were positive for cancer after being on thyroid for periods varying from about a month to as long as eight months. The disease in these patients was often not intensive, but it displayed exactly the same pattern as the disease which had been removed at the first operation, at the time of total thyroidectomy, and was very close to it. These were papillary cancers, and so far, there

has been no evidence of acceleration of spread as the result of the procedures employed. This kind of experience makes us wary, clinically speaking, of the value of thyroid extract as the sole means of controlling the growth and spread of thyroid cancer.

We have also carried out entirely inconclusive clinical experiments on the possible effect of thyroid on other nodules of the gland. This is similar to our experience at our clinic in treating patients with nodular goiter for many years at a time. This was done when Dr. Walter W. Palmer was Chief of the Thyroid Clinic. Ultimately treatment of these goiters by medical measures was abandoned and we concluded that surgery was the method of choice in these cases.

In connection with this point, there is a question I would like to ask Dr. Crile. From the clinical point of view how can the concept of the role of the pituitary as the principal factor in the origin and control of thyroid cancer be reconciled with the extremely low incidence of cancer in non-malignant glands made hypothyroid by surgery?

DR. CRILE: Well, you know there is quite a difference of opinion on that point because Williams and several others have indicated that there is a definitely increased incidence of cancer of the thyroid in those who have been subjected to operations for nodular goiter. Even in the group that you reported from the Presbyterian Hospital, there were several patients who, in a long range follow-up after removal of benign tumors, developed a malignant goiter. In other words, the question is not whether removal of a nodular goiter is protection against the subsequent development of cancer. It is whether it actually increases that tendency.

MODERATOR SLOAN: In our experience with patients with simple non-toxic goiters, many of whom were made hypothyroid for varying periods of time, we have so far found no cancer developing. It was the patients who showed adenomas or neoplasms of the non-malignant type in their glands who subsequently developed cancer, and it was a very small number. There were only two out of ten, as I recall it, in patients who had previously had adenomas, who developed cancer. That is our only experience.

Are there questions that the members of the panel would like to ask?

DR. FRANTZ: I would like to ask Dr. Crile if he really suggests this therapy for a nodule whose nature he does not know?

DR. CRILE: Yes, absolutely. That is exactly what I do suggest. If I know its nature, if I believe that that is a malignant tumor, then I will remove it if it is operable, and I think I can recognize or strongly suspect, up to 90 per cent, between 80 and 90 per cent of these cancers. I am not speaking of the incidental pathologists' cancers. According to the Mayo Clinic's figures on serial section at autopsy, 3 per cent of all persons have microscopic cancer of the thyroid. But it is not about these that I am talking. I am referring to clinical cancers for which the operation is performed. Of these I believe I can recognize between 80 to 90 per cent and, if you like, I am willing to gamble on the other 10 to 20 per cent because I believe that, if I cannot recognize them, they are of such a low undifferentiated order that 50 per cent of them would never give any trouble if nothing were done about them, and the other 50 per cent, or probably the majority of them, would be susceptible to control with thyroid therapy. In our part of the country at least, our best estimates are that, assuming you would really remove nodules from everyone who has them, the mortality, as a result of the operation, would be fifty times greater in our population than the number that might possibly be saved even if one obtained a 100 per cent cure rate for the low grade cancers.

DR. RAWSON: Did I understand you correctly: You do operate those 80 per cent that you do recognize as cancer?

DR. CRILE: Oh, yes. I don't want to have any misapprehension about that. I don't believe the decision should be made by the average person who is not used to thyroid cancer, and not particularly interested in it. I believe it should be made by somebody with clinical experience in thyroid nodules. If the evidence is in favor of its being cancer, it should be operated on by all means.

DR. RAWSON: In patients that you do treat with thyroid, if no shrinkage of the tumor is noted, do you then operate?

DR. CRILE: Oh, no, because it would be much more apt to shrink if it were cancer than if it were a benign adenoma, so to me the shrinkage is evidence of malignancy.

DR. RAWSON: That is evidence of malignancy?

DR. CRILE: I think so.

DR. RAWSON: As I understand it, you do see a shrinkage of a Hashimoto's struma on treatment with thyroid?

DR. CRILE: Yes.

DR. RAWSON: Sometimes a Hashimoto's struma presents itself as a single nodule, does it not?

DR. CRILE: We miss very few of those now. We have learned how to recognize and test them.

DR. RAWSON: I am aware of that, and I admire your approach, but do I understand you to say that if you see shrinkage of this you feel it is evidence of being cancer?

DR. CRILE: I think it is more evidence of that than it is of benign adenoma because, consider the difference between shrinkage of cancer of the prostate, experimental hyperplasia, under estrogens; consider the difference between normal tissue involution and cancer involution. When you have a susceptible cancer what happens is that, just as you grow a strain of bacteria in penicillin, it finally becomes dependent upon penicillin, and if you are growing these tumors and they are dependent upon thyrotropic hormone they eventually become absolutely dependent on it and if you take it away they involute, while normal tissue won't completely disappear.

DR. WERNER: As a matter of fact, about half of our nodules that did shrink were operated on because the shrinkage came to a halt. The decrease occurred early and then stopped. As yet we have had no instance of malignancy.

DR. CRILE: It takes a great many because, after all, there are not many malignant nodules.

DR. WERNER: Mere shrinkage alone does not—

DR. CRILE: Some of them will shrink, but the ones which disappear I strongly suspect of being cancer.

MODERATOR SLOAN: *Knowing the long natural course of this disease and its routes of spread, do you really think that you are justified in proposing the administration of thyroid alone or in combination with surgery as the sole method of treatment of thyroid cancer?*

DR. CRILE: There has not yet been reported any clear evidence of escape from control once established.

MODERATOR SLOAN: Except that the patients that you have reported on have been small in number and over a relatively short period of time.

DR. CRILE: But we have some that go back 20 years from Dunhill's and ours, some of them from eight to ten years, and these girls have perfectly clear chests, and they were all filled up with papillary cancer

before.

MODERATOR SLOAN: But we know, for example, that there are some patients with thyroid cancer, although there have not been very many, who, under treatment with testosterone, have shown just about as striking and dramatic effect as with the administration of thyroid.

DR. CRILE: One, I remember. I don't remember any other.

MODERATOR SLOAN: We have treated four patients using testosterone, and in three of those four there was striking symptomatic relief; in two of them there was some evidence of actual structural change in the tumors. It is not as dramatic as these cases that you have shown, nevertheless that effect has been reported, and of course there was the one case of Lemon to which you referred, in which there was actual healing of the metastases as evidenced by x-ray examination.

DR. RAWSON: Dr. Starr described a case to me this week in which he saw healing of a metastatic lesion on treatment with testosterone. There are only a few such cases but there are some.

MODERATOR SLOAN: Very few of them have actually been treated that way as far as I know.

DR. CRILE: Were any of them in women?

DR. RAWSON: Starr's case was a woman.

MODERATOR SLOAN: Ours were all women.

DR. WERNER: I want to ask Dr. Rawson, do you think that the so-called hormonally non-dependent cancers of the thyroid would be ameliorated by hypophysectomy?

DR. RAWSON: I don't know. We have done hypophysectomy in only one patient who had a very aggressive, advanced Grade III to IV carcinoma of the thyroid, who had liver metastases. We did not alter the course of that patient's carcinoma of the thyroid. I would prefer to choose the patient that I would expect to respond to hormonal changes for that type of experiment.

DR. CRILE: May I comment on that? I think that is very important, because we have not seen the slightest flicker of response in these bad tumors where you need it most. That is the same all the way through, whether it be in Green's transplantation experiments to the chamber of the eye or these hormonally dependent tumors. In general, the ones which give the best surgical results and which tend to metastasize mostly regionally and are not wide disseminators are the endocrine dependent tumors. In other words, it goes right with differentiation. As a result,

we are able to control many of these rare papillary carcinomas which get out of surgical control, because it is the exceptional papillary cancer that is not completely arrested by surgery. If we have been able to control those, I have high faith that the ones which are, say, solitary non-metastasizing papillary carcinoma, would behave in an even more sensitive way than these relatively benign ones which do appear to be controlled.

DR. WERNER: I wonder if I have understood correctly from your discussion that you believe that the tumors during the lifetime of a single patient go from hormonal dependency to hormonal independency, if they are not treated with thyroid?

DR. CRILE: No, but there are seven patients cited in the literature in whom there is documentation of change of tumor type from long standing, slow growing, highly differentiated, and even functional tumors, which after induction of hypothyroidism, by one means or another, have exploded and at autopsy have been undifferentiated. The first one of these was reported by Dr. Frantz.

DR. FRANTZ: That patient was not rendered hypothyroid at any time.

DR. CRILE: Yes, that was one of your early radioactive iodine patients, according to the report.

DR. FRANTZ: It was studied radio-autographically. We had so little I^{131}, on account of World War II, that the dosage was minimal. Her metastases were maximal. They were all functional, and she was never hypothyroid. She had many, many years—

DR. CRILE: What had you done to her thyroid proper? You had done something to her thyroid.

DR. FRANTZ: We had done something. At St. Luke's Hospital they had removed a small nodule seven years earlier.

DR. CRILE: You made the distinct inquiry—I am quite certain you did something to her thyroid—you made the distinct observation there that in your long clinical experience you had not seen a tumor of this histology persist for 20 years. I am speaking about the autopsy pathology.

DR. FRANTZ: She was the first case from which I learned, as Dr. Crile told you, that in the natural history of this disease there sometimes comes a point in which the tumor changes its biological and histological characteristics. That does not always happen, and we have had a

number of autopsy studies in which disseminated disease remained true to the primary type. One of the reasons we know so little about thyroid carcinoma of this kind is that it is a very slowly progressing disease, and just try to get the patient back into the hospital for terminal care, particularly the voluntary hospital, or the university hospital! Attack the resident staff and say, "Would you not like to readmit this person to the hospital on a free basis? We will take care of her until she finally dies, but perhaps you won't get the autopsy!" Most of these patients die at home, and autopsies are very few. But from that one experience in 1943 or 1944, I thereafter made a very great effort to follow patients, even into the casket on some occasions, to see whether I could find out how often these tumors did change character. Quite a number have done so. After a long, long life history of apparently remaining Simon pure biologically and histologically, they have become much more malignant and they have not *all*, Dr. Crile, been hypothyroid.

DR. CRILE: I don't think they have to be. The mild compensated hypothyroid with excess TSH can achieve the same result as a short, severe period of myxedema but it is astonishing how many have changed within two years of the time that hypothyroidism has been induced.

DR. RAWSON: I would like to come back to your comments on eye transplants. Actually the only really successful study with thyroid cancers transplanted to the eye was that one reported by Brown Dobyns. When we were both in Boston together we attempted, a number of times, to get thyroid cancers to grow in the guinea pig. We finally succeeded in transplanting a highly malignant, giant and spindle cell carcinoma of the thyroid into the guinea pig's eye. To me the most exciting thing based on that observation was the later study carried further by Dr. Dobyns and published by him only two or three years ago, when he sub-transplanted those eye transplants of the original thyroid cancer, and carried them through 16 generations. He observed in his sub-transplants every type of histologic pattern of cancer that we find in the human thyroid. This makes me wonder if it may not eventually be possible also to exert some hormonal control over the highly malignant neoplasm of the thyroid. However, there were some benign lesions which, contrary to Dr. Green's prediction, did grow in the guinea pig eye.

MODERATOR SLOAN: *I am afraid that we will have to bring this panel*

session to a close. A number of questions that have been asked have already been answered. One interesting question is: After all is said, what does each panelist do in a 20 year old girl, with a solitary nodule 1 cm. in size, and no lateral cervical glands? Dr. Rawson, what would you prescribe?

DR. RAWSON: In a 20 year old girl with a single nodule, I would look on that with considerable concern. Very honestly, I do give thyroid to those in whom I am not convinced it is carcinoma, and I follow them for three months. Unless it disappears I have them operated on.

DR. FRANTZ: I would be willing to observe a single nodule in an older patient for three months on thyroid, but in a 20 year old I would be tempted to find out what it was. I think we should make it clear that none of us are in disagreement with Dr. Crile, if we can repeat his work, that anything that will deal adequately with disseminated disease in the lungs or bone is a great boon to the patient whose life can only be prolonged or palliated. What we are frightened of is making a cancer become smaller but still remaining as a potentially distributing focus at some distant time. It is the primary that I dread to see treated with thyroid extract.

MODERATOR SLOAN: Dr. Werner?

DR. WERNER: I agree with both of the preceding panelists. I think the introduction of the age factor of 20 years brings out the fact that solitary nodules in younger people carry an even greater likelihood of cancer than do those in older people. I think, however, if one is not clinically suspicious of cancer, thyroid should be given for two to three months. Then if the nodule does not disappear or show definite signs of shrinkage, contrary to Dr. Crile, I would have her operated upon.

DR. CRILE: I would do exactly the same: Give thyroid, and if it does not go away or get a lot smaller, operate on her, but I would not worry as Dr. Frantz does. I would just impress on this woman she must keep taking thyroid for the rest of her life, as she should do even if she has the nodule removed.

DR. FRANTZ: I am delighted to have her take it after it has been removed, in excessive doses too, but I would like to get that potentially metastasizing primary cancer out of that girl, or that woman.

MODERATOR SLOAN: That is the thing. I would vote for its removal because I believe that, knowing the long natural history of the disease,

I would not trust the subsequent treatment at this stage of our knowledge to the administration of thyroid.

Can thyroid medication cause cancer of the thyroid? Does anyone of the panel think it may?

And I should like to ask another question: Does anyone on the panel think that thiouracil will cause thyroid cancer or the administration of propyl thiouracil, or any of the other agents which produce hyperplasia? Dr. Rawson?

DR. RAWSON: I don't think there is any evidence to suggest that. When we were treating a large number of patients with thiouracil, some were followed for a year or so, then finally operated on. In a period of about a year we picked up six patients who had histologic evidence of carcinoma of the thyroid. I think three of those had positive pretracheal nodes. In going back over the material at the clinic, there were similar patients who had been prepared for operation with iodine. The incidence of cancer was not very much different in the different series. I doubt that thiouracil played any role.

MODERATOR SLOAN: *Anyone else?*

I know there have been cases reported in the literature of the association of thyroid cancer with thiouracil treated glands and of course there are other aspects to it. I think one would be much interested in knowing about the incidence of cancer in the progeny of a patient who is given thiouracil over a long period of time particularly when this is associated with a strong familial history of cancer, because, experimentally, the production of cancer requires the presence of a carcinogen. I believe we must assume this to be true also in the case of human beings. What the mechanism is, however, remains obscure.

I regret that we shall have to close this meeting. I should like very much to thank the members of the panel, and to thank you for listening to us.

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ERRATA

In Vol. 35, January 1959 number of the Bulletin,
page 52, line 22, there appears the following sentence:

". . . , indicate that it is probable that the virus is just there as a contaminant from tracheal secretions."

The sentence should read:

". . . , indicate that it is *improbable* that the virus is just there as a contaminant from tracheal secretions."

page 53, line 12, there appears the following sentence:

". . . , the cases we have lost have not been those which have been primarily influenza virus pneumonia."

The sentence should read:

". . . , the cases we have lost have not been those which have *had the bacterial sequelae, but rather those which* have been primarily influenza virus pneumonia."

(Words italicized were omitted from the sentences as originally published).

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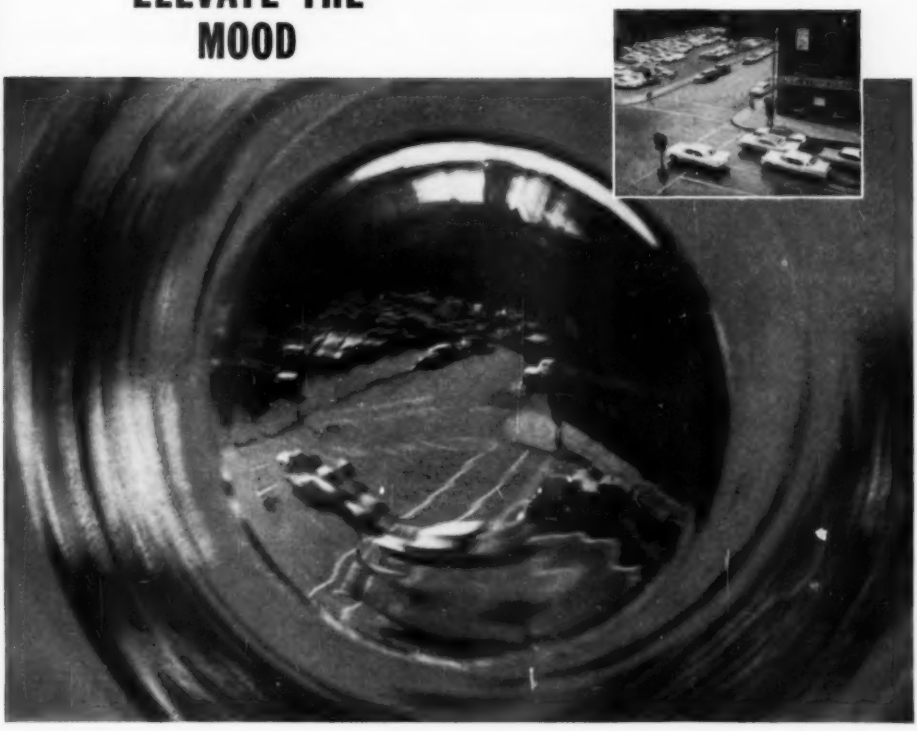

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March 12—THE FUTURE IN NUTRITION—James M. Hundley, *Chief, Geographic Disease Studies, National Institutes of Health, Bethesda, Maryland; formerly Nutrition Adviser to UNICEF from the Food and Agricultural Organization, United Nations.*

March 19—GENETIC CONTROL OF VIRAL FUNCTION—Francois Jacob, *Director The Pasteur Institute, Paris, France.*

March 26—PROBLEMS OF THE ELDERLY PATIENT—Frederic D. Zeman, *Chief of Medical Services, The Home for Aged and Infirm Hebrews, New York*
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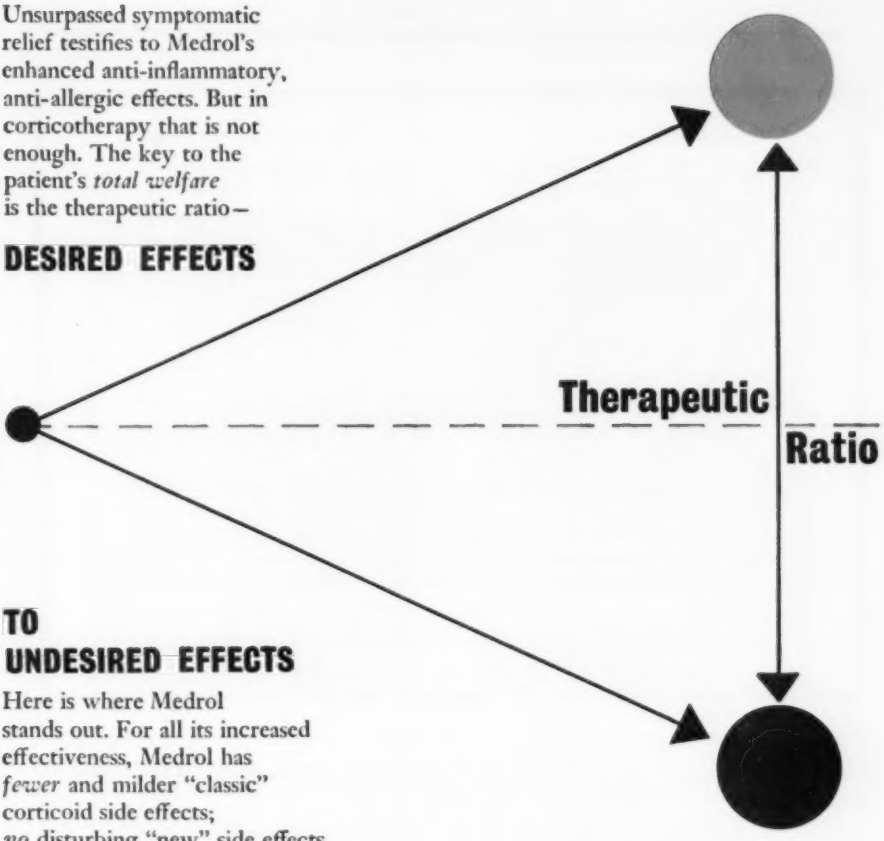

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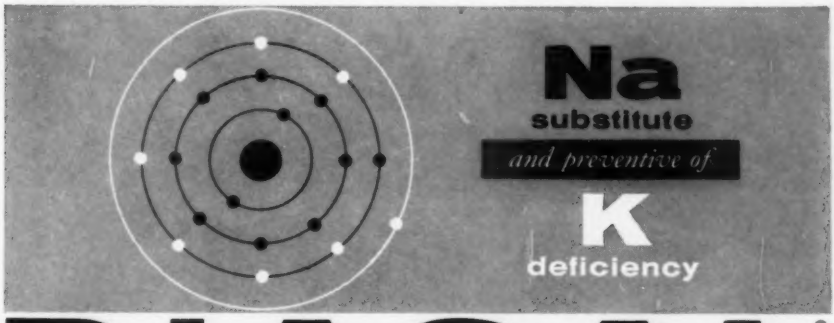

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